SCIENTIFIC MISCONDUCT IN BREAST CANCER RESEARCH

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON
ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

APRIL 13 and JUNE 15, 1994

Serial No. 103–143

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SCIENTIFIC MISCONDUCT IN BREAST CANCER RESEARCH

WEDNESDAY, APRIL 13, 1994

HOUSE OF REPRESENTATIVES
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
Washington, DC.

The subcommittee met, pursuant to notice, at 10:05 a.m., in room 2123, Rayburn House Office Building, Hon. John D. Dingell (chairman) presiding.

Mr. DINGELL. The subcommittee will come to order.

Today the subcommittee will examine a number of important issues associated with serious falsification and fabrication of data in some of the Nation's most important clinical trials on the treatment and prevention of breast cancer, the National Surgical Adjuvant Breast and Bowel Project, NSABP, led by Dr. Bernard Fisher of the University of Pittsburgh.

A particular focus of this hearing is the Federal Government's response to these problems. This case has major implications for thousands of patients who have participated in NSABP studies for decades, for the American taxpayers who have funded NSABP studies in amounts in excess of $100 million, and for maintaining the public trust in the integrity of science.

Regrettably, this is only the latest in a series of cases that the subcommittee has felt it necessary to examine. The subcommittee's involvement in examining, investigating and monitoring the handling of cases of scientific misconduct dates back to 1988 when the subcommittee held its first hearing on the issue.

Many in the scientific community have resisted outside scrutiny and others have sought to minimize the problem. But as we see today, scientific misconduct is a very real problem that requires an intensive and aggressive response by the scientific community itself and by the Federal Government. The case before us is a vivid reminder of how poor the response of the scientific community can be and how serious consequences may be when the scientific community and the Federal Government fall down on the job.

It is, I think, without necessity that the Chair points out that involved in this matter is not only the confidence of the country in science, the questions of expenditure of public money, but the peace of mind of literally millions of women in the United States who feel great concern about the possibility of cancer and the consequences to them of bad science.

Before we get into the specifics of this case, the Chair would like to point out that we will hear today important reassurances for

American women, and we believe that is good. According to the National Institutes of Health, the National Statistical Analyses by the National Cancer Institute, NCI, contractor indicate that the major findings of the NSABP lumpectomy/mastectomy study remain valid even without the inclusion of the fraudulent data. However, because recent revelations have shaken confidence in the entire study, the Chair notes that audits are both necessary and under way to confirm the validity of the remainder of the data in the NSABP database.

What this case shows, however, and what should continue to be of concern to all Americans are major problems in the handling of this matter by all concerned. Patient records were falsified and fabricated for over 13 years before NSABP's initial discovery in June of 1990 of data discrepancies at Montreal's St. Luc Hospital. There was no follow-up until September 1990, when Pittsburgh sent two staffers to Montreal, who not only confirmed this discrepancy but identified a number of others. In December one of the NSABP audit staffers wrote a memorandum describing that on two occasions St. Luc had continued to report follow-up on patients who had been dead for 6 to 8 months.

I have had signatures on petitions which were filed against me by candidates of people who were dead, but I assumed that went on in politics and not in science.

At the beginning of December 1990 Dr. Fisher told Dr. Poisson, who led the questioned work, that he had a data problem and that NSABP was sending a team to Montreal to investigate. Despite talking with the target of the investigation, Pittsburgh and Dr. Fisher still had not disclosed the problem to NCI.

In February 1991 Pittsburgh sent its audit report to Dr. Poisson at St. Luc at which time he confessed to falsifying and fabricating records. About a week later Pittsburgh formally notified NCI of the fraud. Eight months had elapsed since NSABP's discovery of the fabricated and falsified data. The Office of Research Integrity, ORI, of the Department of Health and Human Services was notified and then began its investigation.

In May 1991 Dr. Poisson admitted his fraud and was debarred for life by the U.S. Food and Drug Administration from performing research involving investigational drugs.

On July 3, 1991, Dr. Samuel Broder, director of NCI, was briefed on the status of ORI's St. Luc investigation in which ORI had found "94 cases involved data falsification or fabrications which can be solidly documented."

Dr. Broder concluded that the fraudulent St. Luc data should be removed, that all previously reported studies should be reanalyzed and the reports published on the reanalysis of the work. Reanalyses have dribbled out over time from Pittsburgh to NCI. However, to this date, some 3 years later, no reanalysis has been published. In fact, the New England Journal of Medicine has stated that it will not accept NSABP's reanalysis manuscript until the audits are completed.

In addition, Dr. Broder concluded that no St. Luc's data should be included in any future publications. However, this was summarily ignored by Dr. Fisher. Dr. Fisher submitted at least 13 pa-

pers that contained fraudulent St. Luc data, of which seven have now been published.

Despite Dr. Broder's call for an immediate reanalysis, Pittsburgh did not present a reanalysis until March 1992. This reanalysis was a simple slide show for the NCI/ORI staff, claiming that the originally published conclusions remained unchanged when the fraudulent data were removed. NCI/ORI accepted this account, and based on the assumption that the public health was not at risk for the next year, NCI/ORI insisted on a blackout of news about the investigation.

Between 1992 and 1994 NCI sporadically, and only halfheartedly, encouraged NSABP to complete a manuscript reporting the reanalysis, to significantly upgrade its audit procedure, and to establish a data monitoring committee. Pittsburgh moved forward at an equally halfhearted pace.

After public disclosure of this debacle, Pittsburgh delivered its reanalysis to NCI in a matter of days. NCI's internal statistician had significant concerns about the adequacy.

Recently NCI discovered NSABP was nearly 1 year behind in scheduling site visit audits and 3 years behind in submitting site visit reports to NCI. Among the audit reports that were submitted there were numerous instances in which significant discrepancies apparently were left without any investigation or other follow-up.

For example, during an emergency site visit to Pittsburgh NCI uncovered a Pittsburgh audit report dated September 1993 which included evidence of serious irregularity at St. Mary's, another Montreal hospital. Despite the repercussions of the St. Luc's fraud, Pittsburgh did not report this new problem to NCI, apparently thereby contributing to the recent removal of Dr. Fisher as principal investigator. Last week ORI initiated a misconduct investigation of this apparently falsified data.

One of the reasons we are here today is that no one followed the direction of the director of the NCI. Top NCI officials ignored the director's instructions. Pittsburgh ignored the directions of its funding institution. In fact, top NCI officials have complained to the subcommittee staff that they could not even get Dr. Fisher to return their phone calls, let alone to take direction from NCI.

This illustrates a central problem identified in numerous subcommittee investigations of scientific misconduct: Who is in charge, the NIH, which is the funding institution, or other funding institutions, or the prominent investigators? NIH's capability and willingness to manage and oversee federally funded research continues to be a key question, and millions of dollars are being spent on this kind of research.

A separate but related matter to be discussed today underlines the importance of disclosing and aggressively responding to problems. Dr. Fisher and Pittsburgh did not adequately investigate deaths involved in the use of tamoxifen in clinical trials under his supervision, nor did they notify NCI and ICI in a timely manner.

Tamoxifen has been widely used in treatment studies for years, but only in the last 2 years has tamoxifen been given to healthy women in a prevention trial. At the time of the initiation of this study there were concerns about side effects, particularly uterine

and other cancers, but not a single death at this time had been attributable to this risk.

However, on June 25, 1991, the first tamoxifen-related uterine cancer death occurred. The death was reported to Pittsburgh on August 5, 1991, but Dr. Fisher claims it took him 2 years to determine the cause of death. He told the staff of this subcommittee that he was unable to obtain the autopsy analysis from the hospital in his study.

In fact, by October 1993 Dr. Fisher was aware of at least four uterine cancer deaths attributable to tamoxifen. Just last Friday the FDA and the manufacturer warned doctors about the increased risk associated with tamoxifen. The company has told the subcommittee staff that it first learned of uterine cancer deaths caused by tamoxifen when it was informed by NCI, not Dr. Fisher, in December 1993.

Both of these matters, the St. Luc false data and the delay in reporting tamoxifen deaths, show that responsible audits and oversight are critical to the maintenance of trust and to scientific progress. The challenge before us is to make the scientific process more open and more accountable without politicizing it or burdening it.

In recent years the Congress has attempted to augment the government's ability to combat scientific misconduct. For example, in 1992 we passed the Generic Drug Enforcement Act, which debars from FDA application-related work those involved in falsifying drug testing data provided to the FDA. In 1993 we passed the NIH Revitalization Act, which requires the development of research integrity, policy and regulations.

These statutes help, but they do not substitute for administrative vigilance by NIH nor do they substitute for awareness and action by the scientific community, which has the first and, indeed, the principal responsibility of policing itself, a matter on which it must succeed or other measures will have to be taken by statute or by other action by the government.

The witnesses today include a woman victimized by breast cancer, representatives of concerned women's health groups, and officials from HHS. These include the director of NIH, the director of NCI, the director of the Office of Research Integrity. The Chair announces with regret that Dr. Fisher was unable to testify, citing health reasons. ICI/Zeneca, the manufacturer of tamoxifen, claimed inability to provide witnesses from the United Kingdom on a week's notice. The committee may be interested in hearing them on perhaps greater notice or perhaps a more interesting hearing at a later time.

We thank the witnesses for appearing before us today and we look forward to their testimony.

The Chair recognizes the distinguished gentleman from Colorado for an opening statement.

Mr. SCHAEFER. I thank the Chair. I really appreciate the Chair holding this hearing this morning.

Americans are perhaps the best informed people inhabiting the earth. CNN brings them news 24 hours a day, and the telecommunications industry's super highways transfer certain vital information at the blink of an eye. But when it comes to making

medical decisions, Americans rely on the integrity of scientific research and the oversight functions of the Federal Government to guarantee that the information being received is accurate and complete.

In this regard, the American people have been let down by the scientific community and representatives of the government. The facts of this case are well known. You can't pick up a magazine or a newspaper without seeing some mention of the fraud that was perpetrated by Dr. Poisson.

While it is hard to believe that research scientists would deliberately falsify data critical to an important study, it is even more illogical that his colleagues in the scientific community seem to have looked the other way.

Perhaps worst of all is the fact that the National Cancer Institute has disseminated incorrect and misleading information that has resulted in millions of American women wondering about the honesty and the accuracy of American science.

Mr. Chairman, there is blame enough to be spread around here and it is important that we identify the individuals and institutions responsible for this disaster and take appropriate actions to assure that it does not happen again. More importantly, however, we must seek to reassure the American people about the soundness of American science.

I understand that, despite press statements to the contrary, the National Cancer Institute has still not conducted a comprehensive reanalysis of the study in question. This is unacceptable. Unacceptable. NCI's tardiness and inaction does a disservice to the hard working members of the scientific community and to the American people who are sponsoring the research.

Mr. Chairman, I want to commend you for holding this hearing and swiftly bringing this matter to everybody's attention. American women are scared, and rightfully so. That is why it is important that we do everything that we possibly can to allay their fears and restore their confidence in American research. I particularly am very pleased to see two colleagues of mine, Congresswoman Snowe and Congresswoman Schroeder, my colleague from the State of Colorado, here today. I thank you, Mr. Chairman and yield back.

Mr. DINGELL. The Chair thanks the gentleman.

The Chair recognizes now the distinguished gentleman from California, chairman of the health subcommittee, my friend, Mr. Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman.

Public confidence in the research of the National Institutes of Health and particularly its National Cancer Institute are as important to scientific progress as the quality of its scientists or the level of its funding. Scientific misconduct, however rare, cannot be tolerated and the impact, particularly upon clinical research, must be remedied quickly.

Responsibility rests with the scientific managers of the NIH to be vigilant and alert to the potential for fraud and the implications for patient care. The response to knowledge of the falsified data from Canada was neither swift nor thorough. The consequence has been understandable concern on the part of breast cancer patients and their families.

I am heartened that the recommendations of the National Cancer Institute regarding the use of breast-sparing procedures remain unchanged. I pray the NCI's continuing audit of the National Surgical Adjuvant Breast and Bowel Project database does not reveal additional cases of misconduct and that the stronger administrative safeguards put in place will deter a repetition of this event. Our mothers, sisters and daughters deserve nothing less.

Mr. Chairman, I want to highlight an additional concern that our subcommittee is reviewing in cooperation with Senator Rockefeller involving the tamoxifen prevention trial. Recent revelations regarding the risk of uterine cancer have resulted in stronger, more explicit labeling changes for tamoxifen.

I believe the NCI's decision to proceed with a prevention trial involving the administration of a potentially toxic drug to otherwise healthy women raises serious ethical questions. Hard questions need to be asked about the adequacy of the informed consent process. We need to carefully scrutinize the planning process used by the National Cancer Institute in initiating this trial.

I look forward to working with you on this matter and I commend you for holding this hearing.

Mr. DINGELL. The Chair thanks the gentleman.

The Chair recognizes now the gentlewoman from Illinois, Mrs. Collins.

Mrs. COLLINS. Thank you, Mr. Chairman. As you know, I have been committed to fighting breast cancer by every means available to us for many, many years. As a matter of fact, I have pressed for better coverage for poor women by seeking to get preventive mammogram screening covered under Medicare for years, having authored the first such legislation way back in 1974. I supported efforts to educate the public about the prevention and early detection through breast cancer awareness months and other kinds of activities that have gone on.

I have also supported standards for quality mammograms and pressed for more attention and funding for research on women's health issues as a whole.

As one who has been active on many fronts in the war against this disease, I must say that it is absolutely disheartening to witness this episode. It is difficult enough to discover that researchers would falsify data that would be used in determining treatment regimens for breast cancer patients around the world, but to learn that every effort and precaution was not taken in rooting out the fraudulent data quickly and completely is truly tragic.

Similarly, I am concerned that all speed was not used to inform the women who have breast cancer and who have the most to lose that there was a problem with this data. This is an even more tragic consequence. These actions have at the very least eroded public trust in the good efforts of the breast cancer research community to realize good treatments and preventions for this very deadly disease.

I am disappointed too that the women have been put through this emotional wringer and outraged that some of the scientific community have insensitively described their anguish as "fretting."

I sincerely hope that this hearing will help us to uncover what went wrong at NSABP and at other points in the system and to determine what we can do to keep it from happening again.

While it is clear that this episode has had an abominable effect on women confronting major decisions about treatment regimens for breast cancer, it is equally clear that researchers in the breast cancer research community who have contributed significantly in the past have sustained extensive damage to their professional reputations. I cannot help but wonder what effect the moratorium on enrolling new participants in clinical trials is going to have on the many other important studies that were being run by the NSABP or the chilling impact this controversy has on new scientists or doctors when they decide which research areas they want to study.

Even so, I understand the importance of airing this issue, because it is critically important, and I think it is the only way that we can regain confidence in the important work of the NSABP and the other government agencies that are involved. Without our oversight, we could find ourselves in this situation again and, worse still, suspect the integrity of the scientific data on which women must make life and death decisions.

Mr. Chairman, I am anxious to hear from today's witnesses and hope that through their testimony we can begin to rebuild some of the public trust in the way the government oversees medical research. I thank you, Mr. Chairman, and yield back the balance of my time.

Mr. DINGELL. The Chair thanks my good friend from Illinois for a very valuable opening statement.

The Chair recognizes the gentleman from Oklahoma, Mr. Synar, for an opening statement.

Mr. SYNAR. Mr. Chairman, thank you very much. I join with my colleagues today in discussing this very important subject. I think it is important that we try to relieve some of the tension and the emotion of this issue and, more importantly, to try to present a front that we are concerned about the research that is going on. Millions of women throughout this country are counting on this government and this Congress to make sure that this happens, and I join with you in this hearing.

Mr. DINGELL. The Chair thanks the gentleman for a very helpful opening statement.

The Chair recognizes the gentlewoman from Pennsylvania, Ms. Margolies-Mezvinsky.

Ms. MARGOLIES-MEZVINSKY. Thank you, Mr. Chairman. Mr. Chairman, I want to thank you especially for holding this important hearing on behalf of all of the women and our families in this country, women faced with breast cancer, our daughters who may face this dreaded disease, and all of the families that must confront the painful decisions in treating this disease.

In my district alone, Montgomery County, women face one of the highest rates of breast cancer in the State of Pennsylvania. Every family that has been sitting around at a dinner table and has had to make the difficult decision about what treatment to choose for our loved ones, be it mother, daughter or wife, deserves to know the truth and the findings behind these government financed studies. When that trust is violated, like it was by the National Cancer

Institute and by the National Surgical Adjuvant Breast and Bowel Project, women and our families in this country have the right to be outraged.

As important, we deserve answers as to why our own government misled us. Women now face even more fear and greater uncertainty because of these recent disclosures that data was falsified and fabricated. Our government must get its house in order and must properly ensure the absolute validity of its own studies. The women of this Nation deserve better, and I am eager to see that we get the facts about the dangers that confront us in order to make informed decisions about our lives in the future.

I am particularly pleased to welcome Ms. Frances Visco from Philadelphia, who is president of the National Breast Cancer Coalition.

Thank you, Mr. Chairman.

Mr. DINGELL. The Chair thanks the gentlewoman from Pennsylvania.

The Chair advises that pursuant to the rules of the committee it is within the discretion of the Chair to permit nonmembers of the committee to make opening statements, so the Chair is going to now recognize the two gentlewomen who are most interested in this in the House, Ms. Schroeder of Colorado and Ms. Snowe of Maine. The Chair will recognize first the gentlewoman from Colorado and then the gentlewoman from Maine.

STATEMENT OF HON. PATRICIA SCHROEDER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Ms. SCHROEDER. Mr. Chairman, I thank you for letting us sit in. Congresswoman Snowe and I are here to thank you and thank my colleague from Colorado and everyone on this committee for calling this hearing. This committee is really one of the beacons of light that the women's caucuses look to.

As I think back, it was about 4 years ago we were in this very hearing room when we first heard from the Government Accounting Office that one more time NIH had not paid attention to its own guidelines and did not have any women in the research models. We thank you for your constant, constant diligence in this area.

But I must say, here we are, 4 years later, and you wonder if these researchers are ever going to catch on. This is a serious integrity issue. It is about a disease that will kill 46,000 women in this country this year and afflict another 182,000, and yet somebody felt, ah, it wasn't that important; they could sit on this falsified data and not do anything with it, and, by the way, it didn't matter anyway because they had some other data.

Is it any wonder sometimes we women think that we are not getting a decent deal and that our health is not being treated with the same respect that other people's are?

I was very pleased to hear Congressman Waxman's concerns about tamoxifen. One more time we find out about that, but there was a great delay from when they knew to when they did anything about it, and so I really have great questions whether this trial should continue. If you lured some women in who didn't sign the consent decrees and they knew it at that time and now they are

going to keep the trial going, I think one more time it is saying we are playing fast and loose with women's health.

I think it is time we say to these researchers there is only one reason I vote for money for medical research, and that is because I think good medical research is going to come around as good treatment; it is not to give them a little sandbox they can play in and do anything they want and not be accountable to anybody and never have to answer any questions.

Somehow I thought this was the ego center of America, but I am beginning to think some of the scientific ivory towers are the ego center of America, because they get Federal money from those of us who give it to them and then they turn around and are absolutely offended that we would ever ask questions about the quality of it. If we can't get quality research that leads to quality treatment, then why are we even spending money for it?

There is absolutely no question that women are beginning not to trust anything the government does. For 4 long years this subcommittee, the women's caucus and many of us have been pounding away trying to get this changed, and for 4 long years it says a lot of people still haven't gotten the message.

Thank you, Mr. Chairman. I'm sure we are all going to work together to find some way we finally do give them the message or shut off their money, one or the other. I thank you for calling this hearing.

Mr. DINGELL. The time of the gentlewoman has expired.

[The prepared statement of Ms. Schroeder follows:]

STATEMENT OF HON. PATRICIA SCHROEDER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Mr. Chairman, thank you for allowing me to join you here on the dias today, even though I am not a member of this subcommittee. I'm breaking away from chairing a Research and Technology Subcommittee hearing, so I hope you'll excuse me if I give my opening statement and run.

As co-chair of the Congressional Caucus for Women's Issues and on behalf of women across the country, I want to thank you for taking women's health seriously. These hearings are a benchmark—they signify the new standards of proof that women are demanding from research that will ultimately determine whether they live or die.

Science has to be accountable to people. Mr. Chairman, because you have been so vigilant in being America's eyes and ears on scientific fraud, I applaud you. But you can't do it alone. We need people who are consumers of this information to have a role in how science is done.

The concept of "checks and balances" must extend to science. Women's experience with the scientific research community is proof of this. It was right here in this committee room 4 years ago that the General Accounting Office released its report saying that the National Institutes of Health was not enforcing its own policy of including women in clinical trials.

That revelation led to a revolution in women's health research. I believe that your work here today on the recent fraud in breast cancer research and the flaws in how scientific research is conducted in this country will lead to another revolution—one in which consumers are part of the decision-making process of how science is assessed.

Consumers are not scientists. We know that. But we are not stupid, either. We don't want lies or sugar-coated results—just information, good information. We do not want to be patronized, especially in issues of life and death.

Let me turn to the specifics of this hearing. The National Surgical Adjuvant Breast and Bowel Project was looking into the survival rates of women with breast cancer who had lumpectomies or mastectomies. The project's 1985 study said mastectomies usually weren't necessary, which meant many women were saved from the disfigurement and trauma of having their entire breasts removed.

And then we found out that a Montreal doctor had falsified some data in the study, devastating the women who had undergone or were considering surgery, and casting a shadow over what little research there was on women's health. As if this weren't enough, we learned that the head of the project, Dr. Bernard Fisher, was aware of this fraud since 1990 and that the National Cancer Institute knew about it since 1991. So, all this time passed without a published reevaluation of the findings.

This is serious business, Mr. Chairman. We're talking about women's lives. We're talking about the integrity of the science behind treatment of a disease that will kill 46,000 women this year and afflict another 182,000. We're talking about research with a conscience.

We're told the fraudulent data didn't affect the results of this and other studies. Even if that is true, it is unforgivable that women's health and well-being should have been treated so cavalierly, or that women should have been so needlessly frightened.

None of this has been helped by the recent developments with tamoxifen, a drug used to treat breast cancer. Once again we encounter the National Surgical Adjuvant Breast and Bowel Project, Dr. Bernard Fisher, the NCI, and delays in informing women about risks. And those risks, as we recently have learned, involve higher incidences of uterine and other cancers, and a possible link between the drug and a DES-like syndrome in fetuses. There have even been some deaths.

The NCI and the National Surgical Adjuvant Breast and Bowel Project knew about this updated data last fall. But that data didn't get incorporated into the informed consent document for the prevention trial, which involves healthy women with no history of breast cancer, until mid-January of this year. There are still some women participating in this trial who have not been informed of these risks. It's questionable whether the trial should even continue.

The bottom line in all of this is that quality of research translates into quality of treatment—and the trust that people place in that treatment. And women have very little trust right now because their research has been compromised, resulting in too many confusing signals.

Your role in uncovering scientific fraud and insisting science be accountable is critical. Giving consumers a role as well would help restore women's trust in the research they have funded with their tax dollars. And I think it would help save lives.

Mr. DINGELL. The Chair recognizes the gentlewoman from Maine, Ms. Snowe.

STATEMENT OF HON. OLYMPIA J. SNOWE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MAINE

Ms. SNOWE. Thank you, Mr. Chairman. I want to join Congresswoman Schroeder in thanking you and Mr. Schaefer for inviting us to sit on the subcommittee today to discuss this very important issue to millions of American women, and I want to thank you for your timeliness in investigating this issue and the circumstances surrounding breast cancer fraud in the research.

I have to say, as Congresswoman Schroeder said, we have been dealing with many lapses in women's health issues. We dealt with a lapse in funding, a lapse in enforcement policy that led to the systematic exclusion and discrimination against women in clinical study trials, and now we are dealing with an ethics lapse, a very serious lapse in a long string of lapses concerning women's health matters.

I have to say that it just shatters our confidence in the medical and the scientific establishment and clearly undermines our trust in our ability to conduct accurate and fair clinical study trials, and it strikes at the very heart of women's fears as to whether or not the clinical study trial process which is the basis upon which we get information about breast cancer, has now been jeopardized.

We spend billions of dollars. That is what we have been trying to do as the Congresswomen's Caucus, to increase the amount of

funding for breast cancer, and we have done that. We established an Office of Women's Health Research at NIH. We galvanized women all across America to be educated and aware of the need to have mammograms, and the medical community, and we have done that. Now we find out that we cannot entrust our health researchers with accurate information and reliable data. It truly is disheartening.

I think women in America, at least in the response that we have had as the Congresswomen's Caucus to the efforts to upgrade women's health funding and put it on a level playing field, finally saw the light at the end of the tunnel, that their needs were finally being addressed and not ignored. Well, that light at the end of the tunnel has sort of been snuffed out by this most recent disclosure.

More disheartening than the fact that the falsified data was included in published studies is the way in which this issue has been handled by our primary research institute. As has been mentioned, it was discovered in June of 1990, but it took 8 months before a report was made by any project official. It took 8 months. And it has been 3 years since Dr. Poisson had admitted the fraud in the first place and 4 years since the discovery of the initial discrepancy. Four years. And it was just 1 month ago that the American public discovered this information.

Why did it take so long to inform the public? Why has it taken so long for the National Cancer Institute to reanalyze this information when in fact they made a request for reanalysis in June 1992 and January 1993? In fact, in October of 1992 NCI apparently admonished the project staff of their audit policy, noting that problems with the St. Luc data went undetected for 13 years and that the project's audit policy contributed to the delay in detecting significant data irregularities.

The real terrifying impact of this research fiasco ultimately is on the victims, those women who have breast cancer, because they are going to be haunted by the notion as to whether or not they have made a correct decision; they are going to question the data, the accuracy of the scientific information, their doctor's recommendation. And who can blame them, Mr. Chairman? How can we allay their fears given this real atrophy of our institutions' medical research abilities, and who can really blame them for doubting what decisions they have made?

In 1992, according to Newsweek magazine, 45,000 women chose to have lumpectomies and 117,000 chose to have mastectomies. It seems to me that these women deserve to know the truthful answers with respect to the choices that they have made. The women of America deserve no less.

Thank you, Mr. Chairman.

Mr. DINGELL. The Chair thanks the gentlewoman.

The Chair advises that we will now qualify our first panel. Our first panel is composed of Ms. Cynthia A. Pearson, program director, National Women's Health Network; Ms. Frances Visco, president, National Breast Cancer Coalition; and Ms. Jill Sigal.

Ladies, if you will please come forward. The Chair would like to welcome each of you for your presence today and your assistance to us. It is much appreciated and we believe that your assistance will enable us to have not only a better record, but to move vigor-

ously forward to correct the concerns that I know you share with us today.

As you know, it is the practice of the committee that all witnesses testify under oath. Do any of you have any objection to testifying under oath?

[No response.]

Mr. DINGELL. The Chair advises in addition to this that it is your right to be advised by counsel if you testify under oath. Do any of you desire to be advised by counsel during your appearances here?

[No response.]

Mr. DINGELL. The Chair advises also that copies of the rules in conformity with the Rules of the House, the Rules of the Subcommittee, the Rules of the Full Committee, the Rules of the House are there in the red and blue books available to you to inform you of your rights as you appear here and also of the limitations on the powers of the committee.

Ladies, if you have no objection to testifying under oath, if you would please each rise and raise your right hand.

[Witnesses sworn.]

Mr. DINGELL. You may each consider yourself under oath. The committee will recognize you in this order. First, Ms. Visco; second, Ms. Pearson; and third, Ms. Sigal. Again, the Chair thanks you for your assistance and cooperation with the committee.

TESTIMONY OF FRAN VISCO, PRESIDENT, NATIONAL BREAST CANCER COALITION; CYNTHIA A. PEARSON, PROGRAM DIRECTOR, NATIONAL WOMEN'S HEALTH NETWORK; AND JILL LEA SIGAL, CONSULTANT, WASHINGTON, DC.

Ms. VISCO. Thank you, Mr. Chairman and members of the Energy and Commerce Subcommittee on Oversight and Investigations. I am Fran Visco. I'm a breast cancer survivor, I'm a wife and mother, and the president of the National Breast Cancer Coalition. I was diagnosed with breast cancer in 1987 and I chose to have a lumpectomy rather than a mastectomy based on my own independent readings and the information and advice given to me by physicians.

On behalf of the National Breast Cancer Coalition and the 2.6 million women who are living with breast cancer in this country today, I want to thank you for your work on breast cancer and for this hearing today. It is an extremely important happening.

A diagnosis of breast cancer carries with it a never-ending sense of unease, of concern and fear. Because of my own diagnosis and my work with the National Breast Cancer Coalition, my life is peopled with women who have heard the words, "You have breast cancer", with their families and friends. We are everyone. We are lawyers, we are scientists, we are Members of Congress, we are teachers, homemakers, mothers and daughters. We are, by and large, a medically sophisticated vocal group who live day in and day out with the threat, the fear and the pain of breast cancer.

About 3 years ago many of us took that fear and we turned outward into a national advocacy movement, and we formed the National Breast Cancer Coalition. Our mission is to eradicate the breast cancer epidemic. Our goals are to increase research and funding, to ensure access for all women, and to increase the influ-

ence of women with breast cancer and other consumer advocates in the decision-making that impacts our lives.

Recently the anxiety and fear with which we live daily has been exacerbated by a barrage of events. First, the unfortunate manner in which the National Cancer Institute announced its decision to change the guidelines for mammography; then the news belatedly announced fraud in the lumpectomy studies; and finally, the uterine cancer deaths from tamoxifen.

No one at the National Breast Cancer Coalition has been untouched by these recent events at NCI and NSABP. Mr. Chairman, we must do more to ensure that these systems that allow this fraud to occur, that allow the information to be kept from the public, are held responsible and corrected.

While we appreciate the fact that it appears as though this time women's health in general and women with breast cancer in particular were not placed in great jeopardy by the deceit and negligence of the scientists involved, we are outraged that the information was kept from the public, from women with breast cancer, from women who had decisions to make, and from other scientists and other scientific institutions, from the physicians who were advising women.

With a diagnosis of breast cancer we find ourselves in a world over which we have very little control. We have to learn a new scientific language. And we do. We have to understand new concepts. And we do. And we are asked to turn ourselves over unthinking, unquestioning to the scientific and medical communities. We do not. Not any longer. We insist on being part of the decision-making that impacts our lives.

The recent barrage of news about breast cancer research and treatment underscores the urgency and necessity of our demand that consumer advocates, that breast cancer advocates have a seat at the table.

The discovery that officials at NCI and NSABP not only knew about the fraud but that they did nothing to make this important information readily available to the public and the scientific communities is the most disturbing fact. This failure to respond has caused advocates to question the level of trust that the public places in these institutions. After the dust has cleared from all the media attention, the congressional inquiries there will still remain a crisis of confidence among millions of women who have been asked to trust the institutions charged with acting in the best interest of our health.

I recognize that Dr. Bernard Fisher was a visionary in the field of breast cancer and that his leadership in the area was in part responsible for the advances that have been made in this disease, and I also recognize the tensions and difficulties faced by the National Institutes of Health and the National Cancer Institute.

I have received a number of telephone calls over the past weeks from members of the scientific community. They want to make certain that we activists understand that we must not, in their words, "Throw the baby out with the bath water", that we must not insist on controls that are so severe that the scientific process is unnecessarily impeded. We know. We understand. But we still must ask these questions. What procedures were followed? Did they conform

with accepted standards? And if they did, are the accepted standards sufficient? And most critically, if the status quo is such that scientific fraud is kept from the public, from other scientists and from our physicians, then the status quo must change.

We understand the need for large clinical trials. We support them; we advocate for them; but we need change. In this situation nothing changed. This information has been available for quite sometime but nothing changed until activists and advocates spoke out, until the Congressional Caucus for Women's Issues spoke out, until you, Mr. Chairman, and this committee spoke out and held these hearings.

We know we must be clear for American women. There are other studies that support the results of the NSABP studies. There are benefits to tamoxifen. And if we have all of the information we need, we can make informed decisions.

I have been told not to overreact, not to question too much. We didn't perform fraud. We didn't neglect to uncover fraud for 13 years. We didn't delay reanalysis of data. We didn't keep information from the public. The scientific community did that, and we have every right and indeed a responsibility to call them to task for this. I'm sitting here. I'm a member of the President's Cancer Panel; I'm a breast cancer survivor; I lead a national breast cancer organization; and I found out about this by picking up the New York Times. And I still don't know what happened, what was reanalyzed, when it was, who did it, who is involved.

The public trust in the system is eroding and we are going to get it back through hearings like this and by letting consumers be part of the decision-making process.

This sorry story reveals a system overly concerned with professional reputation and institutional ego, both public and private institutional ego. And while the participants shuffle to position themselves to best protect themselves and to point a finger at someone else, I ask them to stop and to look at me, look at all the women in this room, all the women in your lives. It is my life; it is our lives that your decisions impact. It is my money; it is public money that you spend. We women with breast cancer, consumer advocates belong at the table. We must be a part of the decision-making, of data monitoring committees, of oversight committees, of study sections.

There is resistance in the scientific community to this. We want to "micromanage their research." We "don't understand." "Science is pure." But we are here spending much time and money to fix impure science and bad decisions. Science is not a concept that exists in a vacuum. It is performed too often in isolation, insulated from the public by individuals, by imperfect people with biases and shortcomings. That is why we need a strong system of checks and balances, oversight, different perspectives that will allow science to proceed unimpeded by ego, fraud and erosion of public trust, and that will occur if consumer advocates are given an informed, meaningful seat at the table.

I recently read in the paper a quote from a top official of NCI who said if a year or two ago he had been able to intuit women's concerns about the NCI and NSABP behavior, NCI would have acted differently. Well, there is a fundamental deficiency in a sys-

tem where a public servant believes he must intuit how the public must react to decisions made by his agency. Had a consumer advocate, a woman with breast cancer been part of the process the public's peace of mind and women's lives would not have been left to the uncertainties of an individual's intuitive ability. This self-imposed separation between public agencies and the public they serve is unacceptable.

We are gathered here today because of a crisis, a fundamental flaw in the systems that are supposed to protect us. I feel very strongly, and I know you share that, that we would do a larger disservice to the women of this country if we did not use this as an opportunity to ensure this does not happen again. Let's make it a matter of policy that consumers, breast cancer advocates are involved at every stage of the research process, from advisory boards to study sections at the agency level, to steering committees, data monitoring committees and IRB's at the institutional and study levels. We have to be a part of this.

I want to thank you, Mr. Chairman and members of this subcommittee. Your work has brought us closer to reestablishing public confidence in our institutions and the scientific process, but I know that I do not want this to be the method of oversight of science.

Thank you.

Mr. DINGELL. Ms. Visco, thank you for your very helpful testimony. We appreciate your presence and your assistance.

Ms. Pearson.

[The prepared statement and attachment of Ms. Visco follow:]

The National Breast Cancer Coalition
a grassroots advocacy effort

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Testimony of Fran Visco

President, National Breast Cancer Coalition

before the

Subcommittee on Oversight and Investigations

April 13, 1994

Thank you, Mr. Chairman and members of the Energy and Commerce Subcommittee on Oversight and Investigations. I am Fran Visco, a breast cancer survivor, a wife and mother, a lawyer and President of the National Breast Cancer Coalition.

On behalf of the National Breast Cancer Coalition and the 2.6 million women who are now living with breast cancer, thank you for your work on the pressing issues of breast cancer and for the opportunity to testify before this Subcommittee.

A diagnosis of breast cancer carries with it a never-ending sense of unease, of fear, of concern. Because of my own diagnosis and my work with the National Breast Cancer Coalition, my life is now peopled with women who have heard the words, "you have breast cancer", with their families and friends, with women and men who have lost loved ones to this disease. We are everyone - we are lawyers, scientists, Members of Congress, teachers, homemakers, mothers and daughters. We are, by and large, a sophisticated, vocal group who live day in and day out with the threat, the fear and the pain of breast cancer.

About three years ago, many of us took that fear and turned it outward, into a national advocacy movement -- the National Breast Cancer Coalition. The Coalition is a grassroots advocacy organization dedicated to the eradication of the breast cancer epidemic. We are made up of more than 270 organizations and thousands of individual women, their families, friends and health care providers.

Our mission is to eradicate the breast cancer epidemic. Our goals are to increase funding for breast cancer research and to help focus the research on prevention and cure, as well as treatment and screenings; to ensure access for all women to health care and to increase the influence of women living with breast cancer and other breast cancer advocates in the decision making that impacts their lives.

Recently the anxiety and fear, with which we live daily has been escalated by a barrage of events: first, the unfortunate manner in which the National Cancer Institute announced its decision to change the guidelines for mammography screening; then, the news, (belatedly announced), of fraud in the lumpectomy studies; and finally, the uterine cancer deaths from the tamoxifen trials.

No one at NBCC has been untouched by the recent events at NCI and the National Surgical Adjuvant Breast and Bowel Project. Mr. Chairman, we must do more to ensure that the systems that allowed this fraud to occur are held responsible and corrected. We are very disturbed to learn the extent of the fraud. While we appreciate the fact that it appears as though this time women's health in general, and women with breast cancer in particular, were not placed in great jeopardy by the deceit and negligence of the scientists involved, we are outraged that the information was kept from the public, from other institutions, and from health care providers.

With the diagnosis of breast cancer, we find ourselves in a world over which we have little control. We must learn a new scientific language -- we do; we must understand new concepts -- we do; we are asked to turn ourselves over, unthinking and unquestioning, to the scientific and medical communities - we do not, not any longer. I know that many members of the scientific community -- and most of those in power -- do not believe that we belong at the table. They tell us their science is "pure" and that our involvement will somehow interfere with their work. They accuse us of wanting to "micromanage" research. The scientific community does not understand: it is not our intent to micromanage what they do or to interfere with the process of research. We have simply learned that when the process is left solely to the scientists, women are not well served. The recent barrage of bad news about breast cancer research and treatment underscores the urgency and necessity of our demand that breast cancer advocates, including women with breast cancer, have a seat at the table.

We are here today because, time after time, it is unclear whether women's health is truly at the center of concern. Certainly Doctor Roger Poisson's fraud is indefensible. What really concerns me though, is how we deal with these problems when they arise.

The discovery that officials at the National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project not only knew about the fraud, but that they did nothing to make this important information readily available to the public is the most disturbing fact. This failure to respond to the breach of scientifically valid research techniques has caused breast cancer advocates to question the level of trust which the public places in these institutions. After the dust has cleared from all of the media attention and congressional inquiries, there will remain a crisis of confidence among millions of women who have been asked to trust the institutions charged with acting in the best interest of our health.

The lumpectomy study at NSABP is an enormous undertaking -- it involves hundreds of international sites. Granted, as the size of any study increases, it becomes more and more difficult to exercise absolutely tight controls. But the problem in this

case is that when it became clear -- years ago -- that the data from this landmark study were false, nothing was done to ensure that women's health was protected. Opportunity after opportunity to correct the false data were lost. It is hard to believe that there was ever any real intent to ensure that women and their doctors were aware of the problems in the study. It frightens me to think when, or if, we would have ever learned the truth if the Chicago Tribune hadn't done its own research.

Unfortunately, the lumpectomy studies aren't the only thing under scrutiny today. The Food and Drug Administration released information last Friday about the dangers of the drug tamoxifen which has been used successfully in women after surgery for breast cancer. Unfortunately, tamoxifen has also been shown to increase the risk of uterine cancer. Six women who were taking tamoxifen to prevent the recurrence of disease are dead of uterine cancer. Currently, healthy women are enrolled in tamoxifen trials to determine if it is an effective preventive agent for breast cancer. Thousands of women are still enrolled in this trial at unknown risk to their lives. I am concerned that once again, efforts will not be made to inform the public about the risks associated with this drug. When NCI develops and tests a drug successfully, there is a large publicity effort, but when studies show unexpected risks, somehow that information gets bogged down in procedure and protocols. Consumers -- women with breast cancer -- are the last to know.

Mr. Chairman, we must ensure that women are informed in a timely manner about the risks they assume when participating in any kind of scientific study. Presumably, lumpectomy studies and tamoxifen trials are undertaken in the best interests of women and their health. But as research goes forward, the best interests of women become secondary to scientific protocol, to bureaucracy, and to preservation of professional reputations.

I have received several messages over the past week from members of the scientific community. The scientists want to make certain that I understand that we should not, in their words, "throw the baby out with the bath water"; that we must not insist on controls that are so severe that the scientific process is unnecessarily impeded. We know. We know. But we still must ask these questions: What procedures were followed? Did they conform with the accepted standards? And if they did, are the accepted standards sufficient? Most critically, if the status quo is such that scientific fraud is kept from the public, from other scientists, from our physicians, then the status quo must change.

I recognize that Dr. Bernard Fisher was a visionary in the field of breast cancer. And that his leadership in this area was in part responsible for the advances that have been made. I also recognize the tensions and difficulties faced by the National Institutes of Health and the National Cancer Institute. But when we concentrate too much power in too few people, we do a disservice to the public. I have seen what individual, professional, and institutional ego can do: those in power get to a point where they become insulated from the public and from the patients they serve.

We are gathered here today because of a crisis -- a fundamental flaw in the systems that are supposed to protect us. But I feel very strongly that we would do a larger disservice to women if we do not use this as an opportunity to ensure justice in the future. We must make it a matter of policy that consumers - breast cancer advocates - are involved at every stage of the research process, from advisory boards to study sections at the agency level, to steering committees; data monitoring committees and IRB's, at the institutional and study level. Women must be a part of the research process if their best interests are to be fully ensured.

Thank you Mr. Chairman and members of the Subcommittee.

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a grassroots advocacy effort

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NATIONAL BREAST CANCER COALITION STATEMENT IN RESPONSE TO NSABP DATA FALSIFICATION

A tenet of the National Breast Cancer Coalition policy agenda is that consumers - breast cancer advocates - belong at every level of the research process, from advisory boards to study sections at the agency level, to steering committees, data monitoring committees and IRBs, at the institutional and study level. To advance this agenda, for the past three years, the Coalition has met with top officials at the National Institutes of Health and the National Cancer Institute, and demanded meaningful representation at every level.

Recent events at the National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project (NSABP) underscore the necessity of including consumer advocates at the table. NCI and NSABP knew for several years of falsification of data that were used in critical breast cancer studies of the efficacy of lumpectomy for certain breast cancers and the efficacy of tamoxifen in preventing recurrence and death from breast cancer, and failed to reveal this information to the public. In fact, a manuscript submitted by NSABP to the NCI journal in January, 1994 included results from an investigator known to have fabricated data.

In response to the public's outcry that information has been kept from it, a top official of NCI recently was quoted as saying that if a year or two ago he had "intuited" women's concerns to the NCI/NSABP behavior, NCI would have acted differently. There is a fundamental deficiency in a system where a public servant believes he must intuit how the public may react to decisions made by his agency. Had a consumer advocate - a woman with breast cancer - been part of the process, the public's peace of mind and women's lives would not have been left to the uncertainties of an individual's intuitive abilities. This self-imposed separation between the public agencies and the citizenry they serve is unacceptable.

The behavior of the NCI and the NSABP have put women's lives at risk. These recent revelations have undermined the effectiveness of the NCI and NSABP and have caused breast cancer advocates to question the level of trust to which these institutions are entitled from the public.

The public funds biomedical research; scientists who perform this research are accountable to the public. NCI and NSABP's failure to disclose these data in a timely manner impinges upon the rights of the patient who is entitled to make her decisions with all relevant information revealed, of the scientist and physician who have a responsibility to the process and their patients, and of the public that funds the research.

The vast amounts of money spent on biomedical research warrant structures that do not consolidate power in the few, but rather foster diversification. Diversification will result in new ideas and approaches and decreased opportunities for development of a "club-like" atmosphere among researchers. This will help to build a system of checks and balances and minimize the possibility of vital information being kept from the public.

The National Breast Cancer Coalition demands an independent investigation of both the underlying falsification of the data submitted to the NSABP and of the failure of NCI and the NSABP to timely disclose information to the public. We demand that the names of the biostatisticians named as investigators by the NCI be revealed immediately and that the nature of their charge be made public at once.

TESTIMONY OF CYNTHIA A. PEARSON

Ms. PEARSON. Good morning, Chairman Dingell, members of the committee. Thank you for inviting us to participate in this important hearing. I represent the National Women's Health Network. The Network is a strong supporter of clinical trial research for women. We remember all too vividly the harm that women suffered when they were treated on the basis of hope or belief rather than scientific knowledge.

When we have a context of that kind of commitment to clinical trial research, we were shocked to find out that those involved in conducting and overseeing breast cancer treatment trials have withheld information about falsified data. We were angry when we learned from the press that the National Cancer Institute and NSABP delayed for over 1 year after a final report from ORI documenting falsified data in NSABP. We were angry when we learned that no reanalysis had been done. In the past NCI has rushed NSABP's results to the public when there was good news. To delay announcing falsification of data within breast cancer trials makes it appear that Dr. Fisher and NCI want the public to know results only if they reflect well on NSABP and NCI.

This disregard for the public's right to know is outrageous. We commend Congress for stepping in when it appears that NCI isn't able to assert its authority. Dr. Fisher was seemingly unable or unwilling to follow NSABP's own guidelines for auditing of data and timely reporting of possible problems. NCI apparently took none of the appropriate measures that would have ensured compliance.

Dr. Fisher's failure to report problems with data in the breast cancer treatment trials and NCI's failure to require compliance appear to be paralleled by their actions with regard to the tamoxifen breast cancer prevention trial. In this prevention trial important information that volunteers and the general public need to know is withheld for unreasonably long periods of time, and when eventually given to women, it is incomplete and misleading.

By withholding information about the effects of the drug used in the prevention trial, NCI and Dr. Fisher are attempting to sidestep a public discussion of the wisdom of continuing this trial.

The breast cancer prevention trial, originally a bad idea, is well on its way to becoming a disaster. The trial was a bad idea to begin with because it wasn't designed to prevent disease—breast cancer—in healthy women. Because it is using a drug—tamoxifen—that is known to have serious side effects, it's an attempt to substitute one disease for another. And now, because of the recent revelations, we find that the risks of tamoxifen are actually much worse.

We believe that if these results which have been withheld were openly disclosed when the trial began that it would not have been approved. We also believe that the new information is enough justification to stop the trial. To let this trial proceed is to watch women die of trust.

We would like to briefly review for you the chronology of misinformation by omission and commission in which Dr. Fisher and NCI have collaborated.

In April 1992, when the trial began, healthy volunteers were given a consent form that was misleading in two very important

ways. It told them the risk of an increased chance of uterine cancer was about three. That risk was based on old data, which Dr. Fisher and NCI well knew more cases had been reported. It also told women, "No deaths from uterine cancer were reported."

In fact, as you said in your introduction, as early as 1991 Dr. Fisher and NSABP knew that a tamoxifen treated breast cancer patient who developed uterine cancer had died, but instead of warning women of this possible risk, the consent form told women that uterine cancers that had occurred were thought to be curable.

After the trial began, Congress attempted to exercise some oversight. Congressman Ted Weiss chaired the Human Resources and Intergovernmental Relations Subcommittee. They held an inquiry and a hearing later in 1992. NIH, led by that time by Dr. Healy, resisted all efforts for that committee to exercise its oversight into the quality of consent that was taking place at the trial and into the scientific basis for conducting the trial. The trial continued as planned.

Throughout 1992 and 1993 reports of different kinds of problems, new kinds of problems with tamoxifen emerged and were reported in the scientific literature. These reports described liver damage, eye problems, skyrocketing estrogen levels in pre-menopausal women, cancers of the gastrointestinal tract, and aggressive endometrial cancers.

Through 1992 and 1993 NCI and Dr. Fisher were strangely silent about the results of the important large tamoxifen breast cancer treatment trial called B-14. That trial had reported in 1991 originally no uterine cancers associated with treating breast cancer patients with tamoxifen. Well, what was happening behind the scenes in 1992 and 1993 was frightening. These researchers knew that from zero the number of uterine cancers had jumped to 15 in the tamoxifen arm of the trial, and 4 of those women had died of their uterine cancers. Throughout all this time women were not notified, doctors taking care of them were not notified, and the healthy women volunteering to participate in the prevention trial were not notified.

Finally, in November 1993 Dr. Fisher informed NCI of the deaths. Over 2 more months passed before Fisher and NCI informed women in the prevention trial. We have calculated that over 600 women were given a consent form that said there were no deaths from uterine cancer after the NCI had been informed about deaths.

This is very disturbing, but unfortunately it isn't even the worst of the misleading information that has been given to women by Dr. Fisher and NCI. Women were given an information update in January 1992. It told them that the increased risk of breast cancer was approximately threefold compared to similar women in a general population.

Well, in fact, on April 6 Dr. Fisher published his study upon which those numbers were based and told the scientific community in the NCI's own journal that the risk he found was 7.5 times as high. Women in the prevention trial have never been told that. They still aren't being told that to this day. They are being given a guesstimate, and a guesstimate that is far lower than the results

of a randomized, placebo controlled, double blind trial, the scientific gold standard for evidence.

I ask the committee to consider, if any of you were volunteering for a research trial, how would you feel if you were told that a risk of a complication was increased by three times and you later found out that a good scientific study had found a risk of 7.5 times?

This pattern of behavior has resulted in the general public being subjected to a smoke and mirror show that prevents a reasoned discussion of whether the trial should proceed.

Because of this behavior on the part of Dr. Fisher and NCI, we have come to the state where Congressional oversight is badly needed. In addition to the types of changes that Ms. Visco has described, which we agree with completely, we also call on Congress to ensure that there is an appropriate review of the scientific basis for the tamoxifen prevention trial, and any appropriate review will have to be conducted by an agency other than the NCI and be composed of a majority of prevention experts, public health experts, not cancer treatment doctors.

The National Women's Health Network believes that this trial should be stopped, the tamoxifen prevention trial should be stopped, and that any objective, independent review will come to the same conclusion.

Peter Latham, a 19th Century physician said that, "Medicines and poisons are oftentimes the same substance given with different intents."

To women with breast cancer tamoxifen is good medicine. To healthy women it may be closer to poison.

Thank you.

[The prepared statement of Ms. Pearson follows:]

Cynthia A. Pearson
Program Director
National Women's Health Network

Adriane Fugh-Berman, MD
Medical Advisor
National Women's Health Network

Good morning, Chairman Dingell and members of the Committee. Thank you for inviting us to participate in this important hearing.

The National Women's Health Network is a non-profit women's health advocacy group. We are financially supported by our membership of 400 local women's health projects and over 17,000 individuals. Our mission is two-fold: to advocate for better federal health policies for women, and to provide women with accurate, useful information which gives them more power in decisions about their health care.

As a natural outgrowth of those goals, the Network has been a strong supporter of clinical trial research for women. We remember all too vividly the harm that women suffered when they were treated on the basis of hope or belief, rather than scientific knowledge. The use of DES in healthy pregnant women during the 1950s and 1960s and the routine use of fetal electronic monitoring in low risk women in the 1980s took place because clinical trials either were not done, or were ignored. Women and their babies were hurt, not helped, by these medical interventions.

In addition to our concern that all aspects of women's medical care be based on well-founded scientific research, the Network has been particularly concerned about women's breast cancer treatment. In the 1970s, surgical treatment for breast cancer was a high priority issue for the newly emerging women's health movement. Radical mastectomy, and the "one-step" biopsy/mastectomy procedure were questioned by activists and authors such as Rose Kushner and Barbara Seaman. American women learned that lumpectomy was an option for women diagnosed with breast cancer who lived in other countries. When U.S. physicians resisted women's requests for lumpectomy, women turned to the research establishment and demanded studies that would convince surgeons that lumpectomy was safe.

Those studies began in the U.S. and other countries in the late 1970s. The researchers brave enough to withstand the disdain of the general surgical community were much applauded by women's health activists. The largest of these trials was coordinated by Dr. Bernard Fisher, head of the National Surgical Adjuvant Breast and Bowel Project (NSABP).

Dr. Fisher was hailed as a hero by many in the women's health movement as well as the cancer survivor community. Now, nearly twenty years later, Dr. Fisher is the same man who has been found to demonstrate such utter disregard for the rights of patients to know the results of research. It may seem ironic that we have come today to criticize the behavior of a researcher whom previously we praised. However, it is vitally necessary that the government act decisively to establish clear standards to protect the public's right to swift and full disclosure of all important research findings, whether good, bad, or embarrassing.

As a consumer group our biggest complaint about the behavior of Dr. Fisher and the National Cancer Institute (NCI) is the delay of over a year in announcing to the public that falsified data were submitted to NSABP. Dr. Fisher and NCI also delayed releasing a

reanalysis of previously published studies. In the past, NCI has rushed Dr. Fisher's results to the public, even before publication, when there was good news. To delay announcing the falsification of data within the breast cancer trials makes it appear that Dr. Fisher and NCI want the public to know results only if they reflect well on NSABP and NCI.

This disregard for the public's right to know is outrageous. We commend Congress for stepping in to oversee when it appears that NCI isn't able to assert its authority. Dr. Fisher seemingly was unable or unwilling to follow NSABP's own guidelines for auditing of data and timely reporting of possible problems with data. NCI apparently took none of the appropriate measures that would ensure compliance.

Keeping consumers in the dark has been a theme of the tamoxifen prevention trial fiasco. Dr. Fisher's failure to report problems with data in the breast cancer treatment trials in a timely way, and NCI's failure to require compliance with standard guidelines for auditing and reporting appear to be paralleled by their actions with regard to the breast cancer prevention trial. We see the same pattern of behavior. Important information that volunteers in the trial and the general public need to know is withheld for unreasonably long periods of time, and when eventually given to women it is incomplete and misleading. This pattern of behavior has important consequences for women's health, and important public consequences as well. By withholding information about the effects of the drug used in the prevention experiment, NCI and Dr. Fisher are attempting to sidestep a public discussion of the wisdom of continuing this trial.

The breast cancer prevention trial, originally a bad idea, is well on its way to becoming a disaster. It is designed to give healthy women tamoxifen, a breast cancer treatment drug, at the same dose taken by patients with cancer. The trial accepts any woman over the age of 35 whose risk of developing breast cancer in the next five years is 1.7 percent. At the time this trial began, the known serious risks of the drug were reported to be almost exactly equal to the volunteers' risk of developing breast cancer. Specifically, uterine cancer and blood clots occurred in 1.8 percent of women who took tamoxifen for five years. The trial was a bad idea to begin with because it wasn't designed to test whether tamoxifen could prevent disease in healthy women, but rather to determine whether one disease could be substituted for another.

Now, we find that the risks of tamoxifen, known to be serious at the time the trial began, are actually much worse. We believe that if the results which have been withheld by Dr. Fisher had been openly disclosed when the trial began that it would not have been approved. We also believe that the new information is enough justification to stop the trial. To let this trial proceed is to watch women die of trust.

We would like to briefly review the chronology of misinformation by omission and commission in which Dr. Fisher and NCI have collaborated.

In April, 1992, when the tamoxifen prevention trial began, women were given a consent form that told them the risk of uterine cancer was increased by about three times based on existing data from several large trials of tamoxifen. Women were told that nine out of

3,097 women on tamoxifen developed uterine cancer versus four out of 3,091 women not treated with tamoxifen. These numbers were based on a 1991 report prepared by an NCI scientist, Dr. Susan Nayfield, who relied upon data supplied by the manufacturer to the FDA in 1990. By 1992, NSABP had reports of four more tamoxifen-treated women who had developed uterine cancer. NSABP included this information in the prevention trial protocol, but did not include these new cancers in the consent form that women were given. If the most up-to-date information had been given to women, they would have been told that the risk of uterine cancer was not three times as likely, but four or five times as likely.

In addition, the 1992 consent form assured women that "no deaths from uterine cancer were reported". Again, the consent form was seriously misleading. As early as 1991, Dr. Fisher and NSABP apparently knew that a tamoxifen-treated patient who developed uterine cancer had died. But instead of warning women of this possible risk, the consent form told women that the uterine cancers that had occurred were "thought to be curable".

The 1992 consent form was misleading in other ways, as well. Women were told that a very small number of women taking tamoxifen might die as a result of blood clots. What they weren't told was that NSABP had found that a much larger number of women suffered life-threatening blood clots which required hospitalization, and indefinite treatment with blood-thinning medication. Also, women were told that liver cancer had been reported in rats receiving tamoxifen in doses greater than the dose used in humans. Women were not told that the manufacturer of tamoxifen had reported to the FDA in a public hearing that the cancer-causing dose of tamoxifen in rats produced levels of tamoxifen in the blood that were equivalent to the blood levels of women taking tamoxifen in all of the NSABP trials.

After the trial began, we were deeply concerned that women were being hoodwinked into volunteering for a trial that put their health at risk. We turned to Congress for help, and worked with Congressman Ted Weiss, who chaired the Human Resources and Intergovernmental Relations Subcommittee of the Committee on Government Relations. The Committee conducted an inquiry into the quality of the informed consent forms used in the tamoxifen prevention trial and found shocking results. Two hundred and sixty eight forms were examined. Sixty eight percent either omitted or altered one or more of the key points from the model consent form approved by NCI reviewers. To put it bluntly, NCI and NSABP had allowed a bad consent form to become worse. Although Mr. Weiss died as the inquiry was completed, his committee held hearings chaired by Congressman Donald Payne in October, 1992. At the hearing, the Committee members attempted to exercise their oversight function by questioning the underlying scientific basis of the risks, the possible benefits of tamoxifen, and the poor quality of information given to women volunteering for the trial. NIH was represented by Dr. Healy at that hearing. Dr. Healy resisted all efforts of the committee and the eventual outcome of the hearing was that a few consent forms which didn't even meet minimum legal requirements for informed consent were improved. But the trial continued as originally planned.

Since the last time Congress reviewed the tamoxifen prevention trial, more evidence about its harm has been published. Liver damage in women on tamoxifen has been reported to regulatory bodies in both the U.S. and Britain. Depression, eye damage and increased rates

of gastrointestinal cancers (including liver cancer) have been reported. Problems with ovarian function in premenopausal women, including skyrocketing estrogen levels and large ovarian cysts, have also been reported.

As these reports accumulated, NSABP and NCI were silent as to any update from B-14, the large tamoxifen treatment trial coordinated by Dr. Fisher. The original results had been published in 1989. No updated information was provided throughout 1992 and 1993, either to the general public, medical journals, or those who received the prevention protocol. We have now discovered that what was happening behind the scenes was frightening. Uterine cancers were being diagnosed at a rapid rate, and more women were dying as a result. From zero uterine cancers at the time of the 1989 publication, to six as of May, 1991, the number jumped to 15 in the tamoxifen treated arm of the study. And still women weren't notified.

Finally, in November, 1993, Dr. Fisher informed NCI of the increased incidence of uterine cancer in breast cancer patients taking tamoxifen, and of the four deaths from uterine cancer. Even after this long delay, Dr. Fisher and NCI allowed months to pass before informing women. Throughout all of 1992 and 1993, women in the prevention trial were being given a consent form that falsely reassured them that uterine cancer was not fatal. Over two months passed after Dr. Fisher's report to NCI before women were informed through an information update. We have calculated that nearly 600 women were given a consent form that said there were no deaths from uterine cancer after NCI had been informed about the deaths.

This is very disturbing, but unfortunately, it isn't the worst of the misleading information that has been given to women by Dr. Fisher and NCI. The information update given to women in the prevention trial in January, 1994 accurately informed women that women taking tamoxifen had died from uterine cancer. However, it also told women that the risk of developing uterine cancer was three times higher than a similar group of women in the general population.

It wasn't until April 6, when Dr. Fisher's uterine cancer paper was finally published in the Journal of the National Cancer Institute that we found out that the risk of developing uterine cancer for women in the NSABP trial was not three times as high, but actually seven and one half times as high. In his discussion, Dr. Fisher attempted to minimize his own results. With NCI's consent, women in the prevention trial were told a "guesstimate" of their risk for uterine cancer that was far lower than the results of B-14. A "guesstimate" that is nowhere close to the risk found in a randomized, placebo controlled trial -- the gold standard of scientific evidence. We would ask the Committee members to consider whether if they were volunteering for a research trial, they would want to be told that the risk of a serious complication was increased by three times, when a good study had found an increased risk of seven.

We can't impute motive to Dr. Fisher and NCI, but it appears as if they don't like the results of the NSABP trials, and so they are trying to avoid others becoming aware of unpopular results. Similar to NCI's acquiescence, Dr. Fisher's unwillingness to publish a

reanalysis of the NSABP trial affected by falsified data, NCI has allowed Dr. Fisher to present women with extremely misleading information about the results of the B-14 trial.

This pattern of behavior has resulted in the general public being subjected to a smoke and mirrors show that prevents a reasoned discussion of whether this trial should proceed. NCI and Dr. Fisher have also refused to respond to scientists with legitimate critiques of the risks and possible benefits of the trial. Last fall, two important reviews of the prevention trial were published by credible scientists in peer-reviewed journals. Neither critique has received a response. To consumer advocacy groups it appears as if Dr. Fisher and NCI don't believe that along with public trust, and public tax dollars, comes a duty to participate in public discussion.

In summary, the National Women's Health Network is convinced that Congressional oversight is necessary in this case. We hope that there will be two results from this effort. We call for an increased commitment by NCI to timely disclosure of all important information from clinical trials. We also call for the establishment of a system to ensure monitoring and follow through of that commitment.

We also call on Congress to ensure that there is an appropriate review of the scientific basis for the tamoxifen prevention trial. Any appropriate review will have to be conducted by an agency other than NCI and include a majority of prevention and public health experts, not cancer treatment researchers. The National Women's Health Network belives that this trial should be stopped and an objective, independent review will come to the same conclusion. Peter Merc Latham, a 19th century physician, said "medicines and poisons are oftentimes the same substance given with different intents". To women with breast cancer, tamoxifen is good medicine. To healthy women, it is closer to poison.

Mr. DINGELL. Ms. Sigal, we are happy to welcome you here today. The time I last saw you at the fund-raiser that we were participating in I was not aware we were going to have you before the committee. I notice you look a little bit uncomfortable. I want you to know that the committee is known for having sharp teeth, but we are also known for being careful on whom we use them. So I hope you feel comfortable and welcome.

TESTIMONY OF JILL LEA SIGAL

Ms. SIGAL. Thank you, Mr. Chairman. I've been in the room when you have exhibited your sharp teeth, so I'm glad I'm not going to get that today.

Mr. Chairman, Mr. Schaefer, members of the subcommittee, my name is Jill Sigal. I reside in Alexandria, Virginia, and I work in Washington, DC., as a consultant. I am 32 years old and just 6 months ago I was diagnosed with breast cancer. My doctors informed me at that time that I had a choice in surgical procedures. I could either have a lumpectomy with follow-up radiation or a mastectomy.

Loss of a breast is a difficult prospect for any woman. Being 32, loss of a breast was an especially frightening option. However, if the choice was between having one breast or accepting a substantially higher risk of premature death, the choice for me would have been a clear one. I would have opted for life.

I spent the 2 weeks between the time of my biopsy and the time of my surgery talking with numerous doctors at various hospitals all over the Washington area trying to gather information in order to make an informed decision. My doctors did not recommend a particular procedure to me. They left the decision up to me. My doctors laid out the facts for me and they told me about one study that concluded that a lumpectomy with follow-up radiation had the same long-term survival rate as a mastectomy. The study that my doctors cited to me is the study that is in question today that we now know includes falsified data, as admitted by Dr. Poisson.

I had a lumpectomy and I based my decision to do that solely on the study that is in question today. Since my surgery I have undergone 6½ weeks of radiation and I am currently in the middle of chemotherapy. I am halfway done.

I learned only 2 weeks ago that Dr. Poisson had falsified data and therefore the results of the study are being questioned. I did not learn about this fraud from the National Cancer Institute; I did not learn about this fraud from the National Surgical Adjuvant Breast and Bowel Project; I did not learn about this fraud from the University of Pittsburgh or from Dr. Fisher. I learned about this fraud because one day I was looking over a friend's shoulder who happened to be reading the New York Times and a headline jumped out at me talking about the breast cancer fraud.

I understand now that there was a notice in the June 21, 1993, Federal Register regarding Dr. Poisson. I went back this week and I read the notice. The notice doesn't even identify the study in question. Therefore, if I had read the Federal Register notice back in 1993, which I am not in the habit of reading the Federal Register, I would not have known what it was referring to because it

didn't mention the lumpectomy study. Reading the notice back in 1993 would have proved to be of no use to me.

My anger and outrage that a doctor could possibly engage in such gross scientific fraud was surpassed only by my disbelief when I learned that the National Cancer Institute, an instrument of the United States Government, knew about the falsified data 3 years ago and deliberately did not give it wide-spread publicity.

I also understand that the University of Pittsburgh knew about the falsified data 3 years ago and deliberately did not give it wide-spread publicity. I also understand that the University of Pittsburgh knew about the fraud approximately 4 years ago, and it withheld the information from the National Cancer Institute for a period of time. These organizations did not inform the public. They did not even inform the doctors who could have then advised their patients accordingly.

How many women during these 3 years made a decision about their surgery, as I did, based on this study. How many women must now wonder, as I do every day, if they will die because they may have made the wrong decision? How many women, Mr. Chairman, will die? We will never know.

If my cancer returns, it is likely to come back in my liver, my lungs, or my bones. My doctors tell me that if this happens, my cancer cannot be cured and I will die. If this happens, my family and friends will never know if my cancer had spread prior to my operation and there really wasn't much that anybody could do or whether the reoccurrence was due to the fact that I had a lumpectomy instead of mastectomy.

I take no comfort, no comfort whatsoever from the fact that the Institute that swept the fraud under the rug for 3 years now claims to have conducted a re-analysis of the study and maintains that the findings are still valid. For me, the National Cancer Institute has forfeited any claim to credibility. Indeed, I understand that when the National Cancer Institute first announced to the public that it had conducted a re-analysis, the announcement was false. It was only later, from my understanding, that a re-analysis was actually conducted, and even then the so-called re-analysis did not include a review of the raw data.

Mr. Chairman, there seems to be no end to the fraud and deception. As a result of the National Cancer Institute's behavior in this manner, I now question other policies of the National Cancer Institute, including its policy that women under the age of 50 should not get a mammogram unless they are at high risk.

Well, Mr. Chairman, I don't think there's a doctor in the world that would say that I was at high risk. In fact, the doctors that are treating me have told me that my chance of getting breast cancer at age 32 was 0.2 percent. My cancer had been growing inside me for several years. If I had had a mammogram a year or two ago, I would have possibly caught the cancer at its earliest stage when it's contained within the duct, and the survival rate would have been for me then approximately 98 percent. Well, my cancer was not caught at this stage. I had invasive cancer, and my chance of survival is far less than 98 percent. If I had had a mammogram earlier, I very likely would not be facing the daily fear of premature death.

Mr. Chairman, there is nothing that this subcommittee can do to help me. My fate is cast, but there are several things that this subcommittee can do under your leadership to prevent similar atrocities from occurring in the future. I'm no expert in this area of breast cancer, but I ask the subcommittee to consider the following recommendations, some of which, based on your opening statement, Mr. Chairman, I understand may be currently underway.

First, I ask the subcommittee to consider commissioning an independent re-analysis of the study and the raw data with a written report to be submitted to the subcommittee within 60 days. The report should be published and made available to the public.

Two, order the release of the raw data with the names of the patients redacted.

Three, prohibit the National Cancer Institute from awarding any grants to the University of Pittsburgh for 5 years, or until after a thorough study of its procedures and safeguards has been conducted.

Four, extend the 8 year debarment of Dr. Poisson from receiving Federal grants to a lifetime prohibition.

Five, change the way allegations of scientific fraud are investigated by the National Cancer Institute and the Federal Office of Research Integrity, including requiring timely widespread notification of scientific fraud.

The fear that arises from facing one's own mortality at my age can at times be paralyzing. Now, as a result of this fraudulent study, and the apparent cover-up by the National Cancer Institute and the University of Pittsburgh, my terror is exacerbated. Today there exists a crisis of confidence and credibility as it pertains to the National Cancer Institute and to the other organizations associated with this study. Even if the conclusion of the study, Mr. Chairman, holds up after a proper re-analysis, think about the agony of uncertainty that I and thousands of others are currently enduring.

I thought I had made an informed decision, and I thought I had done everything in my power to increase my chances of enjoying a normal life expectancy. Now, I must wonder every day if I really have done everything to maximize my chances of survival.

If the members of this subcommittee can save just one life, then in my very humble opinion, you will have accomplished a lifetime achievement as a member of the House of Representatives. That life you save may be somebody you know. I do not understand how I got breast cancer, but I've come to accept it, and I deal with it as best I can. What I cannot understand and cannot accept is why a medical doctor would falsify data in a study that was intended to guide thousands in making what could be a life or death decision, and why the people given the responsibility to oversee the study did not publicize the fraud immediately.

I would like and need answers to these questions, Mr. Chairman. To me, this hearing is not just about breast cancer. To me, this hearing is about accountability. The people have a right to have faith and confidence in U.S. government sponsored research. These recent events show us clearly that the process has failed. Mr. Chairman, you and your committee have the authority and the

power to diminish or eliminate the possibility of this atrocity from ever happening again by changing and strengthening the process.

Mr. Chairman, Mr. Schaefer, thank you from the bottom of my heart for holding this hearing and for doing what you can to correct this grave injustice.

Mr. DINGELL. Thank you, Ms. Sigal, for your most helpful statement. Be assured that we intend to pursue this matter with the usual vigor that this subcommittee has displayed over the years, and I would say that there are a number of people out there who probably will rest poorly being aware of that information. I will observe parenthetically that we will anticipate hearing from the University of Pittsburgh. I know they're looking forward for a chance to come forward and tell their side of the story, as we are looking forward to a chance to hear their side of the story and perhaps ask them a few simple little questions.

Ms. SIGAL. Well, I take great confidence in that, Mr. Chairman. Thank you very much.

Mr. DINGELL. Well, be assured we will follow this matter forward vigorously.

Ms. SIGAL. Thank you, sir.

Mr. DINGELL. Your statement has been most impressive, and we thank you for your assistance.

Ms. SIGAL. Thank you, Mr. Chairman.

Mr. DINGELL. The Chair is now going to recognize members of the committee in the order prescribed by the rules. The Chair recognizes first the gentleman from Colorado, Mr. Schaefer.

Mr. SCHAEFER. Thank you very much, Mr. Chairman. I do appreciate the testimony of all three members before the committee today. We know that a dreadful situation has developed, not only with the people involved but the Cancer Institute, and I think we're all very interested in getting to them a little bit later on. I would ask Ms. Sigal, you testified that you first learned of the falsifications of the research data from news reports. Is that right? Your doctor did not know?

Ms. SIGAL. No. I was reading over a friend's shoulder who was reading the March 27 edition of the New York Times, and this headline, "Federal Officials to Review Documents in Breast Cancer Study", jumped out at me. That's the way I found out about it. I went to my doctor after I read this and I asked him if he knew. He found out about it the same way, reading about it in the paper.

Mr. SCHAEFER. Ms. Visco?

Ms. VISCO. Mr. Schaefer, that's exactly how I found out about it, and I think——

Mr. SCHAEFER. By the newspaper?

Ms. VISCO. By the newspaper. I think it's particularly egregious, you know, my organization in October presented the President with 2.6 million signatures on a petition from women and men and children across this country asking for a national action plan for breast cancer, and the President said yes. At his request, Secretary Shalala hosted a conference of the National Institutes of Health on December 14 where we had consumer activists, government representatives, scientific community representatives, private industry, the media, and representatives from Congress, come together

to sit at a table and begin the design of a national action plan, and we shared ideas and facts and concepts.

I feel quite foolish today thinking back on that day because I thought we were there at the table on a level playing field, and I find out there was very important information that was kept from us. If it was ever going to be told to us, even belatedly, it should have been that day, and it was not. So yes, I found out about it from the newspaper.

Ms. PEARSON. Mr. Schaefer?

Mr. SCHAEFER. Yes?

Ms. PEARSON. I read the Federal Register each day. Maybe I'm one of the few, but it's part of my job. I look at the table of contents and then I read the notices specific to women's health, and even I couldn't find it. That notice in June was buried. There was no way any reader could tell its importance.

Mr. SCHAEFER. Don't you think—is there any responsibility on the physicians themselves to look at this? I mean, your doctors, they should have been at least told of what was going on, it seems to me. How can they advise you, even though they give the final decision to you on whether you have a lumpectomy or a mastectomy? Shouldn't this data be submitted to them on a continual basis?

Ms. SIGAL. Absolutely, Mr. Schaefer. I mean, without this information being given to the doctors, the doctors can't advise people like myself adequately. I mean, my doctors did a great job. I'm very proud of the doctors that are caring for me, and they gave me the best advice they could and they laid out the facts as we knew them back then in October, just 6 months ago. If they had had this information, I would have seriously considered whether or not the risk was worth it of going through with a lumpectomy, and I probably would have gone forward. As difficult as it would have been emotionally for me, I probably would have had the mastectomy in order to maximize my chances of living, because that's what this is all about.

Mr. SCHAEFER. Ms. Visco, how long was it ago that you have a lumpectomy?

Ms. VISCO. September 1987.

Mr. SCHAEFER. And you have gone back and been checked over this period of time?

Ms. VISCO. Yes.

Mr. SCHAEFER. And there hasn't been any recurrence or anything?

Ms. VISCO. I have not been diagnosed with a recurrence, that's correct.

Mr. SCHAEFER. Well, we're all glad of that. I know you are.

Ms. VISCO. Yes.

Mr. SCHAEFER. But again, it's a decision that you made at that time, in 1987, and so it's worked out all right.

Ms. VISCO. I understand the studies. I understand that there are independent studies that support the results of the NSABP sponsored trial. I understand that. I think most women with breast cancer do understand that, but we do live every day with the threat of a recurrence hanging over our heads because we don't know how to cure this disease. That level of concern is with me every single

day, and now on top of that, I have a new level of concern. It's unnecessary. It doesn't need to be there. This information—I'm sure there's fraud. I mean, you cannot guarantee that there's never going to be fraud, but once you find out about it, do something about it.

Mr. SCHAEFER. I think this is right. My time is about up here, Mr. Chairman, but I think Ms. Sigal hit it right on the head. We're not only talking about this particular study and what the Cancer Institute has withheld or who has withheld what. We're talking about trust in the government on what information they disseminate to the people. I think this is the bottom line that chairman wants to get at. I too would like to do that. So, I certainly appreciate your testimony here today, and we'll do all that we can in working with the chairman to make sure this does not ever happen again.

Mr. DINGELL. Will the gentleman yield to the Chair just very briefly? I just want to make a comment. We have gone through these questions of scientific misconduct, fraud and things of that kind. One of the things that's been most comforting to the Chair has been the wonderful, cooperative way with which all of my colleagues on this subcommittee have cooperated with the Chair in these investigations, particularly the gentleman from Colorado. It has been—we have had great difficulties, as the gentleman very well recalls. The committee has been under attack for having insisted that the question of scientific misconduct and scientific fraud be addressed internally inside the scientific community, and also that Federal agencies address their question and the responsibility.

We've also dealt with it up until now from the standpoint of the concern that we had and the jurisdictional responsibility we had about the funding with Federal dollars. Today, because of the comments of Ms. Sigal, Ms. Visco, and Ms. Pearson, we're seeing it now from a more personal standpoint, from the hurt, the danger, the peril, the trauma that it occasions to citizens who, interestingly enough, are taxpayers who support these programs, who are entitled to openness and truth, who are entitled to honorable and proper behavior by investigators, and proper discipline within the scientific community and within the government itself. Regrettably, we're not seeing that, but my comments to the gentleman particularly are my gratitude to him and the members of the committee. My commendations to him for the faithful and vigorous and decent way in which he has stood with the Chair as we've gone through some very hard times in these investigations. So, I express my thanks to the gentleman at this time, as I do to the rest of the members of the committee.

The Chair recognizes now the gentlewoman from Illinois for questions.

Ms. COLLINS. Thank you, Mr. Chairman. Ms. Sigal, I must say that your testimony was most impressive, and one that I don't think I'll ever forget. I certainly can't say that of a great many others that I have heard, not on this subject but on any subject as a matter of fact. Let me say that I think that you have done the country, and particularly those of us who are interested in this matter, a tremendous favor by coming to us and giving us your personal testimony on what has happened as a direct result of the in-

formation that you did not have to avail yourself of regarding a treatment that you could have chosen, and I personally thank you for that. We all have a debt of gratitude that we owe you.

The chairman has already said that we're going to have people in from Pittsburgh to answer some questions about why this was not revealed to you and to many other people, and we're also going to receive testimony at this hearing and the others from the NIH and the NCI. They would have us to believe that the issue here is simply probably that the conclusions of the lumpectomy/mastectomy trial are still valid. Do any of you at the table think that the conclusions are still valid?

Ms. PEARSON. This is interesting, Ms. Collins, because in the 70's, lumpectomy was something that women demanded. We heard that it was available to women in other countries. They seemed to be surviving as long, but American surgeons resisted. So we, and some in the cancer research community called for trials, and that's why I opened by saying what a strong supporter we were of research. We were delighted that the lumpectomy trial began in the United States, and when it reported the results, we joined the National Cancer Institute in encouraging women to consider lumpectomy. We know that there were five other trials conducted independent of NCI and NSABP, some in other countries, that have found similar results.

So, if the NCI and NSABP had had the sense and just the decency to come forthrightly immediately and say we found this fraud. It's horrible. We'll make sure it never happens again, here's our re-analysis. We think our trial is still the same, and there's these five other trials. Women would have had some worry, of course, but it could have been handled much more usefully if we had gotten the whole package of information all at once. Now it comes out as if there's a cover-up, and it's hard for women to even get the information that there are several other trials that show lumpectomy as effective as mastectomy.

Ms. VISCO. I echo what Ms. Pearson said. I also want to add that I think the fact that fraud was going on for 13 years and the fact that whatever procedures were in place were unable to detect that, and the fact that the NCI wasn't aware of that for quite some time, that has to be put into the mix also. Although we do recognize that there are other studies reporting the result, the concern in the public trust is affected. When you look at that and say well, what else is out there? If these are the procedures and they didn't work here and they got caught here, what else is out there that we don't know about? We need to do something about these procedures.

Ms. COLLINS. Exactly. Ms. Sigal?

Ms. SIGAL. Mrs. Collins, first of all, thank you very much for those kind remarks. I think it's premature to say whether the conclusion of the lumpectomy study is still valid. I personally have a big problem with anything the National Cancer Institute has said and probably will say today. It's not going to comfort me. As Ms. Visco said, this has been going on for 13 years. I think what needs to be done is we need to have a proper re-analysis of the study. I don't take their word for it. I can't because my life is depending on this, as well as hundreds of thousands of other women. So, for them to tell me, oh, you're going to be OK, that doesn't mean any-

thing to me today. I don't think it means anything to my sister who's sitting behind me or my mother, who's watching. No, we need to have a proper re-analysis and a review done.

As regards to the other studies, when I made my decision, I never knew that other studies existed because my doctors, I assume, felt that the study in question today was the pre-eminent study and that is the only one that they told me about. It wasn't until last Friday when I went racing to my doctor to talk to him about all of this, when I went to have my chemotherapy treatment, that he said well, Jill, there are other studies that exist. Well, but I share Ms. Visco's view. Well, if it could happen in one study, maybe it could happen again. I don't want to believe that. I do want to have faith in what government sponsored research tells us, but I think there's a credibility gap. I think with your help and the chairman's and this committee's, that you could fix that.

Ms. COLLINS. Thank you. Ms. Visco, NCI and HHS officials have expressed their concerns about due process and fairness. They believe it was best to not tell the public about the unreliable St. Luc's data until after the conclusion of the ORI investigation. Have you thought about whether HHS could have preserved fairness while also honoring the public's right to know and what strategies might HHS have pursued in this regard?

Ms. VISCO. Yes. As a breast cancer survivor and as an attorney, I did give that quite a bit of thought. The process should not have taken that long. The information could have been released to the public much earlier. Simply, the investigation should not have taken that long. Dr. Poisson admitted falsifications. In addition, the NCI had the information and the investigation was complete, I believe the latest date I've heard is last spring, the spring of '83. We're just finding out about it today, and from the newspaper. So, I do believe that whatever process is in place to investigate has to be shortened, and I'm certain that it can be.

Ms. COLLINS. Thank you. Thank you, Mr. Chairman.

Mr. DINGELL. The Chair thanks the gentlewoman. The Chair recognizes now the gentlewoman from Pennsylvania, Ms. Margolies-Mezvinsky.

Ms. MARGOLIES-MEZVINSKY. Thank you, Mr. Chairman. Ms. Sigal, today we hear testimony that in 1992, NCI and HHS officials failed to recognized that Dr. Fisher had not re-analyzed his data showing the recurrence of a tumor in the ipsilateral breast for ladies that had had a lumpectomy. But these same NCI/HHS officials have told subcommittee staff that the absence of re-analysis of this data was not important because occurrence of ipsilateral tumors is a secondary variable, a minor consideration they said. As a women who just 6 months ago had a lumpectomy, what's your reaction to this kind of thinking?

Ms. SIGAL. Well, it may not be important to the people in the National Cancer Institute, but I can tell you it is certainly important to me and to my family and my friends, who don't want to see me die because of this. So, my reaction to your statement is, I think that's an outrageous thing for the National—and inhumane thing for the National Cancer Institute to say. It's that kind of attitude that I think has led to this problem. I think people's egos have gotten in the way of scientific integrity in research, and I believe that

there has to be some kind of reviewability for these scientists. If there's nothing to hide, then why not open up the process?

Ms. MARGOLIES-MEZVINSKY. What did your doctor say to you?

Ms. SIGAL. My doctor tried—I was there on Friday when I had my treatment, and I was quite upset. He said that there are other studies. Like I was telling Mrs. Collins, I did not know about that at the time when I made my decision to have a lumpectomy in October, but he said that there are other studies and that everything is going to be OK. Well, I have great faith in my doctor, I really do, but I would greatly appreciate if we could have a proper reanalysis because until that is done, until it is done by some entity that's not connected with the National Cancer Institute, yes, I will still worry. My family will still worry, and I'm sure that thousands and tens of thousands of women who are out there in the same position that I am will worry as well.

Ms. MARGOLIES-MEZVINSKY. Did your doctor say anything about Dr. Fisher?

Ms. SIGAL. Yes, he did. He was actually very complimentary of Dr. Fisher. I personally can't speak to Dr. Fisher. I don't really know much about what he has done except for what I've read in the papers, and it does sound very good, but yes, my doctor was very complimentary of him. In fact, he even said, "We don't need to throw the baby out with the bath water." He did say that. I looked at him and, quite frankly, while I was getting shot up in the veins during my chemotherapy treatment, we had quite a heated discussion about this whole subject for the hour that I was there. I'm not sure in this particular instance that I agree completely with what my doctor thinks in this instance, but I do have faith in the way he's treating me.

Ms. MARGOLIES-MEZVINSKY. If Dr. Fisher and his colleagues were here today, is there any message that you would like to share with them over and above what you said in your testimony?

Ms. SIGAL. I'm not sure there's a message that I'd like to send, but there are certainly questions that I would want to ask Dr. Fisher, like why. I want to know why. I want to know why the process broke down. I want to know why the procedures weren't followed, their own procedures, the procedures of the National Cancer Institute and the National Institute of Health. I want to know why the audits weren't conducted over the last year because I don't understand. Is there some scientific reason? Did somebody's ego get in the way? I don't know, but that's what I'd like to know from Dr. Fisher and the University of Pittsburgh. Why did he allow this to happen?

Ms. MARGOLIES-MEZVINSKY. The other panel members?

Ms. VISCO. I would like to speak for a moment to an issue that you raised earlier, and that is the fact that there apparently were some findings of recurrence but not mortality, and they were not considered statistically significant. This also speaks to the position that my organization takes, and I know that Ms. Pearson's organization also supports, and that is we women with breast cancer and consumer advocates should be involved because I have been to a number of meetings where the scientific community has spoken about what they're looking at is the mortality rate.

We keep raising the issue of well, what about recurrence? What about quality of life? What about these issues? Mortality, how many women live and died is not the only question we should be looking at. In this trial, let's look at the women who had lumpectomies rather than mastectomies. How many recurrences were there? Those are not questions that the scientific community have asked. If women were at the table, those questions would be asked.

Ms. PEARSON. I guess what I would say to Dr. Fisher is that he seems to have lost the understanding that with public funds and public trust needs to come a commitment to public discussion. As I described in my testimony, there's been an apparent pattern of behavior of believing that Dr. Fisher, NSABP and to some extent the NCI, can decide for themselves what the public needs to know and what they're willing to talk about with the public. I would just want to let Dr. Fisher know that we disagree strongly with that.

Ms. MARGOLIES-MEZVINSKY. Thank you. Mr. Chairman, I yield back the balance of my time.

Mr. DINGELL. The time of the gentlewoman has expired. The Chair recognizes now the gentleman from Ohio, Mr. Brown.

Mr. BROWN. Thank you, Mr. Chairman. Ms. Pearson, is it possible for NCI/HHS to regain the trust of the public, particularly the trust of women at risk for and diagnosed with breast cancer?

Ms. PEARSON. I think it is, yes, because if they can't we're in big trouble. We'll never have scientific grounding for our treatment decisions, and we know that we desperately need that. I think NCI and HHS need to take the suggestions of the National Breast Cancer Coalition and put advocates who are representing and report to consumer groups at the table at all the important stages on the study sections, on the review committees, on the policy setting boards. I think they also need to make a commitment that is backed up by policy, by systems, by procedures, to disclose fully and quickly the results of clinical research, whether they're good, bad, or embarrassing.

I think if the NCI demonstrates a willingness to take these steps instead of doing as it appears they've been doing in the press for the past few weeks, just defending themselves, I think they can regain our trust, and I hope that's the outcome.

Mr. BROWN. Ms. Sigal, can they regain that trust?

Ms. SIGAL. Well, I'd have to say right now I'm probably one of the National Cancer Institute's biggest critics, biggest skeptics, but I agree with Ms. Pearson. I think it's essential to regain the trust, and as I said in my statement, it's not just about breast cancer. It could be a study about heart disease, about diabetes or AIDS, but it's essential to have trust and credibility in the National Cancer Institute, the National Institute of Health, and any government sponsored organizations. So, I would hope that could be re-established, but I think it needs to be a different attitude at the National Cancer Institute, and hopefully as a result of this hearing and Mr. Chairman's efforts, that maybe the National Cancer Institute and National Institute of Health and the efforts of the subcommittee members, maybe they'll understand why this is so important. Statistically it may not be important to them, but it sure is important to me and to thousands of others.

Mr. BROWN. Ms. Visco, in addition to a change of attitude at NCI, what steps must they take to regain the trust of people all over the country?

Ms. VISCO. Well, I echo Ms. Pearson's support of the National Breast Cancer Coalition's demands, including consumer advocates, but I want to add something to that. The Coalition's position has been from the time we heard about this that we need an independent investigation and an independent analysis of the data. We were told at first there was a re-analysis. Then we heard that there really wasn't a re-analysis and then we're not certain what was actually analyzed or re-analyzed. The public trust has eroded completely in that area, and we do need an independent analysis of what happened. I think that would go a long way toward helping restore trust.

Mr. BROWN. Ms. Pearson, what went wrong at Pittsburgh in the NCI involving the Poisson matter and the refusals and delays and re-analyzing lumpectomy/mastectomy data after the fraud at St. Luc's? What actually went wrong?

Ms. PEARSON. Well, I have to just tell you my opinion, and I'm someone who's seen Dr. Fisher in action at a few meetings. I've had a lot of interaction with NCI officials. As you've heard, Dr. Fisher was hailed as an important key researcher in women's breast cancers for many years, and deservedly so. Our founders, in fact, and some of our early leaders wrote praises of him in books designed for the lay audience.

I believe that what happened over the 80's was a subtle shift in power, to the point where Dr. Fisher, because of his deserved eminence and respect for his research, began to be more important than those who technically funded him and oversaw him. We heard the chairman say that it got to the point where he didn't even return NCI's phone calls. I knew he wasn't returning mine, and that wasn't a real big surprise, but to hear that he wouldn't return Dr. Broder's phone calls is shocking to me.

That's what I think happened, but somehow the NCI's funding process keeps going back to the proven producers. Instead of having a process that brings in new blood, fresh ideas, new researchers who will have to be accountable to those who fund them, they rely too much upon Dr. Fisher's proven track record and let him grow in power until he thought he didn't need to be accountable to them or his own rules.

Mr. BROWN. What are other scientists and researchers saying about what you just said? Are they echoing that?

Ms. PEARSON. Most of the conversations I've had with other scientists and researchers are very casual and informal. I have heard echos of that kind of sense of what's going on, that Fisher was in a way untouchable.

Mr. BROWN. Thank you, Mr. Chairman.

Mr. DINGELL. The time of the gentleman has expired. The Chair is under the discretion that by the rules, the Chair is now going to recognize first the gentlewoman from Colorado for questions and then the gentlewoman from Maine. Ms. Schroeder?

Ms. SCHROEDER. Mr. Chairman, you have been so generous, and we really thank you for letting the co-chairs be here. I just want to be very brief because I don't want to take the time, but one of

the questions I have for NCI, and I think that's what you're saying when we talk about trust, is they seem to be saying, you as consumers and you as people who are trying to monitor this, are really too stupid to be in at the beginning of this process when they asking the questions, framing the questions, and everything. But all of a sudden you became very bright at the end of the process. When you look at mammograms, they're saying hey, we at NCI can't really decide. We'll just have women sit around and read this and decide whether or not they need it.

So, it's amazing how bright we come from the beginning. They don't want us playing in that sandbox when they're giving out the money and framing the questions you want addressed in the research and monitoring. Then when the research comes out, and obviously they haven't been monitoring the research too well, they kind of say gee, we're confused. Now, if these bright scientists who know how to hand out the money become very confused at the end and don't know how to hand out the recommendations, we got a real problem with attitude. Am I hearing you right? Would trust help if you could get in at the beginning? It's a little confusing to be told you're so bright at the end after you've been shut out at every single level.

Ms. VISCO. Absolutely. I mean, there's no question that would go a long way, and probably what would be one thing that would go the longest way, in addition to this type of hearing, to restoring public confidence is letting consumers in at the very beginning and giving us a seat at the table.

Ms. SCHROEDER. That's right, and I think that goes to the arrogance that we're hearing. I know I think of myself as fairly well informed, but I'm really rather enraged when they say sit down and read the data and you make the decision whether you would need a mammogram between the ages of 40 and 50. Please. I mean, are we all to go back to medical school, or what are we supposed to do? That doesn't make any sense to me. Cindy, I had a specific question to ask you that you may or may not want to answer, and that's on the tamoxifen trial. As you know, there are very many, many healthy women enrolled in the current study. As we now know late, one of the side effects has been it can cause birth defects.

How confident are you that this trial, the women in this trial, the healthy women in this trial, have been notified of that, have been told to get birth control, or are there hospitals or doctors who don't believe in birth control participating that may not tell them that part. Have you looked at that, because another thing about research is getting people willing to be in the research things. If this type of thing goes on, and we'll have that group of women sitting at the table saying how could they have known and not told us and gotten consent reforms, and we don't want a repeat of the horror of DES?

Ms. PEARSON. That's right. I'm not completely confident that the 11,000 healthy women who enrolled in the prevention trial before this—that it's in right now have been adequately informed about the risk of birth defects with tamoxifen. As I mentioned briefly in my testimony, Congressman Ted Weiss, before his death, conducted an inquiry into the quality of consent that was being given to par-

ticipants in the trial. His staff reviewed 268 forms from 268 different centers. Twenty-six percent gave inadequate information about the need to use birth control and the types of birth control which were appropriate to be used in the context of this study.

Upon questioning at the hearing that was chaired by Mr. Payne, the response of the prevention staff was well, you know, some of the Catholic hospitals are involved, and we can't tell a Catholic hospital what to tell women. Now, we agree 100 percent, Catholic hospitals are religious institutions, but they don't have the right to participate in a trial where women's safety and the safety of unborn children depends on their knowledge of the need to use birth control and the appropriate kinds.

Because of Dr. Healy's resistance to that committee's oversight, we have no information about whether or not those 26 percent of the participating centers have fully complied with the need to give women all of the important information.

Ms. SCHROEDER. Mr. Chairman, that may be something we may be able to find out through your committee because if that is still going on, I would say stop the trial immediately. I mean, that's outrageous if there are women who are not getting the full consent, and let's hope they are.

Thank you very much, and I thank you, Mr. Chairman.

Mr. DINGELL. The Chair thanks the gentlewoman. The Chair is going to have the staff look into this matter. The Chair recognizes now the gentlewoman from Maine.

Ms. SNOWE. Thank you, Mr. Chairman, and I want to thank all of you for your very compelling testimony, and Ms. Sigal, I know we're not in your shoes, but we certainly share your agony. In listening to your testimony, I couldn't help but think that I would approach the issue and the trauma of making such a decision just the way in which you did, based on information that my doctor would provide and asking questions, and hopefully getting accurate answers. I just truly regret that this has happened. We just want you to know that we share what you are going through.

Ms. SIGAL. Thank you very much.

Ms. SNOWE. What can we do now, immediately, to restore confidence? I know we've talked about placing a consumer advocate, for example, at the table, and I think that's a very important issue, and I want to get to that in a moment. What can we do immediately to restore confidence, because I am concerned about what you're going through, and there are thousands of other women who are going through the same crisis right now. It's a crisis of confidence in knowing whether or not you made the right decision. Would it be an independent re-analysis as soon as possible?

Ms. VISCO. I feel that would be a very strong statement to the American public. If the National Institutes of Health and the National Cancer Institute recognized, not saying they are incapable of it, but recognizing the erosion of public trust and because of that, stating that they recognize the need for an independent analysis and joining with this committee in asking for and in making that happen.

Ms. SNOWE. I think that we definitely should insist on it because I don't think there's any other way to restore the confidence on this issue given the series of terrible errors and misjudgment in ethics.

I think we have an obligation to do that, and it's something that we should do. Have you heard, Ms. Visco, from other women across the country as a result of this study?

Ms. VISCO. Yes. We've heard from quite a few women across the country as a result of this study. I will say that most women do recognize the existence of other studies, and they have read in the papers that the results of the NSABP study will not change, but they are still concerned. On an intellectual level, you understand that. On an emotional level, you can't accept it.

Ms. SNOWE. Exactly.

Ms. VISCO. And that's where they are.

Ms. SNOWE. And that's where they are. So, a number of women are aware of what has happened based on press accounts?

Ms. VISCO. Oh, absolutely.

Ms. SNOWE. And obviously the only way they're finding that out is as you all did here.

Ms. VISCO. Right.

Ms. SNOWE. In a letter to the co-chairs of the caucus from NIH, it talks about the re-analysis that was requested of Dr. Fisher. Is it amazing to you that given the fact that they already knew that there was a serious breach of ethics and falsification of data, that they would go back to the individual who's responsible for conducting this clinical study trial to do the re-analysis, and just to assume that it's going to be done. Obviously he didn't do it. They requested—they made this request on numerous occasions, and obviously he ignored their request, which is just staggering to me that somehow the NCI had no ability to enforce this re-analysis on a timely basis.

Should we not make sure that there's an independent cooperation any time that there is a problem and question about the accuracy of the data?

Ms. VISCO. Yes, absolutely, I agree, especially after this episode. Perhaps if this episode had been handled differently, we'd have a different answer to that question, but I think in light of recent events, absolutely we'd need it, as part of the process.

Ms. SNOWE. Because I am just amazed that Dr. Fisher would, for whatever reasons, refuse on numerous occasions—I mean, there were so many time lags between the time they identified the discrepancies and the time in which they received any official report, and then it was sort of tucking this all into the Federal Register in a very brief statement in hopes that no one is going to identify it or catch it. I mean, that was obviously the intent because everybody knew then that something was seriously wrong here that they wanted to go unnoticed, but they wanted to be on record that somehow they had identified this problem and they made public recognition of that problem.

What are the next steps that we should take? You were mentioning having an advocate in the process. Recently, I co-signed a letter with Representative Towns asking for a consumer advocate on the consensus panel for ovarian cancer. Is that what you're talking about as well?

Ms. VISCO. Yes.

Ms. SNOWE. And at the beginning stages of the process, should that be by statute or should it be by regulation?

Ms. VISCO. I'm not certain it can be by statute. I believe it should be policy of the National Institutes of Health and the National Cancer Institute, that when Federal money is being spent—we're working on getting this done on a private institutional level also, but you can be instrumental in helping us make it happen on a public level, that consumer representation belongs at the table study sections, data monitoring committees, oversight committees, not just advisory boards.

Ms. SNOWE. Well, the reason why I asked whether it should be done by regulation or statute is because we had a problem with the fact that women were excluded systematically from clinical study trials, and actually, NIH was violating its own policy. It was not enforcing its own policy. So, I have mixed feelings about whether or not that should be done by regulation or statute so that we have the assurance that it is being done and that we don't have to go through the process of determining whether or not it's being enforced or not, that we know by statute they are required, and obviously we understand that there could be problems there, too, but it's obviously going to be much harder for them to contravene public law.

Mr. BROWN. Absolutely. When you're handing out money on a Congressional level and on a National Cancer Institute level, you certainly have the power to make as a condition to being eligible for that money, the fact that a consumer representative must be involved.

Ms. SNOWE. Well, thank you all very much.

Mr. DINGELL. The time of the gentlewoman has concluded. The Chair would like to express my personal thanks to each of you for your valuable assistance to the committee. Your help has been of great importance to us in developing our record. The Chair advises that the questions that you have raised, including the chronology of events, will be brought to the attention of witnesses from the NIH. The Chair excuses the panel members with our gratitude. We also wish you, Ms. Sigal, great good fortune.

Ms. SIGAL. Thank you very much, Mr. Chairman.

Mr. DINGELL. And you also, Ms. Visco. I want to extend in addition to that my personal thanks. Thank you very much, ladies.

Ms. SIGAL. Thank you, and thank you, Mr. Schaefer.

Mr. DINGELL. The Chair announces the next panel. The panel will be composed of Dr. Harold Varmus, Director of the National Institutes of Health, and Dr. Samuel Broder, Director, National Cancer Institute. They will be accompanied by Dr. Bruce Chabner, Director, Division of Cancer Treatment, Dr. Michael A. Friedman, Associate Director, Cancer Therapy Evaluation Program, and Dr. Lyle W. Bivens, Director, Office of Research Integrity. Gentlemen, thank you for being with us today. We express the thanks of the committee to you for your presence. The Chair advises that, as you know, the practices of the committee are that all witnesses who testify before the committee testify under oath. Gentlemen, do any of you have any objection to testifying under oath? Very well, the Chair advises that if you do testify under oath, it is of course your right to be advised by counsel in the course of your appearance. Do any of you desire to be advised by counsel as you testify under oath?

[No response.]

Mr. DINGELL. Very well. The Chair advises that copies of the rules of the subcommittee, rules of the committee, rules of the House are there at the witness table before you in the red and blue books to inform you of your rights and limitations on the power of the committee as you testify before us today. Gentlemen, if you have no objection then to testifying under oath, would you please each rise and raise your right hand?

[Panel sworn.]

Mr. DINGELL. Gentlemen, you can consider yourselves to be under oath. Gentlemen, we will recognize you beginning with Dr. Varmus, then Dr. Broder, and then by Dr. Bivens, and then by the others as you might find it necessary or might suit the needs of the hearing. Doctor, you are recognized.

TESTIMONY OF HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH; SAMUEL BRODER, DIRECTOR, NATIONAL CANCER INSTITUTE, ACCOMPANIED BY BRUCE CHABNER, DIRECTOR, DIVISION OF CANCER TREATMENT, MICHAEL A. FRIEDMAN, ASSOCIATE DIRECTOR, CANCER THERAPY EVALUATION PROGRAM; AND LYLE W. BIVENS, DIRECTOR, OFFICE OF RESEARCH INTEGRITY, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. VARMUS. Mr. Chairman, thank you. Before I proceed with my prepared statement, I would like to say a word or two about the transition in mood that will accompany the development of this panel. We've just experienced an emotionally trying discussion by three women who have all been affected by or are involved in the ramifications of the breast cancer studies that we've talked about. Ms. Sigal's testimony was particularly impassioned and moving. We're going to now move into a more analytic mode to discuss the process by which the current events unfolded.

As we do that, I think it's important to realize that although we are five men at this table responsible for some of the events that we want to explore and for their oversight, it's important to remember that we, too, have a deep, passionate involvement in these issues. In my own case, my mother and my grandmother died of breast cancer. I've devoted most of my research career to the pursuit of an understanding of breast cancer. I have dear friends who are making the kinds of decisions Ms. Sigal and Ms. Viscoe were describing. I feel a deep responsibility for the research that leads to the ability of women and their physicians to make such decisions.

We have to recognize as well that as the previous panel indicated, we're talking not just about gender issues and breast cancer, we're talking about all of the research that's affected by NIH. We're talking about events that could have affected a study of prostate cancer or lung cancer or other diseases that are rare or common. We take these responsibilities very seriously, and as we engage in this discussion and proceed to a detailed analysis of how we've responded to the events that you've heard described, that although we analyze these, the passion that you've heard in the previous panel is shared my many of us.

That being said, Mr. Chairman, we welcome the chance to appear before you today to discuss the disturbing events that have been well described here in the previous panel and by yourself and in the press that involve the clinical studies of breast cancer carried out over many years by the NSABP under the sponsorship of the NCI. Before I introduce Dr. Broder, the Director of the NCI, who will provide a detailed account of these events and his efforts to respond to them, and before we introduce his colleagues and Lyle Bivens from the Office of Research Integrity, I would like to outline what I hope we can accomplish during this panel.

First and foremost, we can reassure women, including Ms. Sigal, who have chosen breast sparing surgery for breast cancer, that they have made a decision that is strongly and unequivocally supported by current scientific evidence, evidence provided by both the NSABP and by many other groups. That analysis has been independently analyzed by the EMMES Corporation, as Dr. Broder will review. We are prepared to submit all the data to independent auditing if that proves to be necessary.

Second, we can summarize the central facts in a complex story that includes a long history of path breaking clinical science by the NSABP, leading to many of the improvements in the treatment of this disease, which regrettably we still incompletely understand. It also includes a well documented episode of flagrant fraud that you've heard discussed at one of its more than 400 participating institutions, and the facts include inadequate and slow administrative responses and insufficient auditing procedures by arms of the government and by the NSABP.

Third, we hope we can describe corrective measures that have been taken in recent weeks by the NCI to improve the administrative functions of the NSABP and to strengthen oversight by the NCI. Such measures should increase the likelihood that fraudulent acts occurring in the conduct of clinical studies will be promptly detected and reported in the future. In this way, we believe that the lessons learned from the current incident can enhance the conduct of medical science supported by the NCI and by the other components of the NIH.

It's important to recognize at the outset that remarkable progress has been achieved in the practice of medicine and surgery in the past few decades. Consider just three prominent examples: The cure of acute leukemia in children by chemotherapy, the reduction in mortality by control of high blood pressure, the prevention of blindness by laser surgery in diabetic patients. In each of these three instances and in many other examples, including the breast cancer therapies under discussion today, progress can be attributed to the formation of large cooperative, multi-institutional and often multinational groups.

The well documented successors of such groups require meticulous planning, coordination, and oversight to insure that protocols are uniformly followed in an often varied and far flung group of institutions. Occasionally, as in the case of the NSABP, such procedures may fail, and the malfeasance of an investigator may go undetected and uncorrected. The hard-earned prestige of productive groups such as the NSABP may even be among the factors that contribute to the deficiencies of monitoring and reporting.

Our discussion today will properly focus not on the act of fraud itself but on the methods for detecting, investigating and publicizing fraud and for evaluating its consequences. The questions we will address are especially contentious and complex when the suspected fraud might affect the outcome of clinical studies and hence might alter the procedures used in medical practice. Under such circumstances, there are profound tensions between the public's need for access to information that could affect people's health and the right of someone accused of fraud to be protected by due process.

The public does not want to be frightened by false accusations. Likewise, the public does not want to be deprived of knowing the consequences of accurate ones. For these reasons and others, as the previous panel has stressed, the prompt resolution of allegations of fraud and the rapid dissemination of findings of fraud in clinical research are matters of great importance to us, and they deserve our attention today and in the future.

It's my hope that this hearing can provide an opportunity to understand what has happened in the current instance and to acknowledge the dedication and integrity of the vast majority of clinical researchers whose valuable efforts may be jeopardized by the recent events. It's an opportunity, most importantly, to reflect upon ways we could learn from this experience to improve what we do to advance the Nation's health and to insure that patients such as those you've heard in the first panel receive the benefits of our efforts as caretakers of the Nation's health.

At this point, Mr. Chairman, I'd like to introduce Dr. Sam Broder, the Director of the NCI, who will give you an account of his institution's response to these events.

STATEMENT OF SAMUEL BRODER

Mr. BRODER. Good morning, Mr. Chairman. Good morning, Madam Chairwoman and members of the subcommittee. I am Dr. Samuel Broder, Director of the National Cancer Institute, the NCI. Accompanying me today on your left are Dr. Bruce Chabner, Director of the Division of Cancer Treatment of the National Cancer Institute and Dr. Mike Friedman, the Associate Director of the Cancer Therapy Evaluation Program. We are very pleased to have this opportunity to follow up on Dr. Varmus's remarks.

I would like to discuss NCI's recent actions following the Office of Research Integrity findings by fraud on the part of a surgeon at L'opital St. Luc in Montreal, and the steps taken by NCI to correct this situation. The oversight and monitoring of clinical trials is vital to insure that research advances are based on sound and accurate data. Honest errors can and do occur, and will always occur whenever human beings are involved in any process. However, fraud is different and cannot be tolerated. We have a responsibility to all cancer patients, physicians, and scientists to validate the integrity of our clinical research.

There is in this country widespread use of breast sparing procedures as an alternative to mastectomy. I am not that old, or I don't think I'm that old, but within my medical school training, there was an era in which women would be informed that they had a biopsiable lesion, would be given a general anesthetic, would have

no option except to go under the surgery, and to not know whether they would awake with a benign biopsy or what was then a radical mastectomy. A medical student in my era who challenged this practice of medicine in that time would possibly face problems with his or her career development.

Today, I assure you, Mr. Chairman, members of the subcommittee, the general public, and physicians, that breast sparing surgery remains an appropriate and safe procedure. I do not come here before you as merely a scientist or government administrator per se, but as someone who knows how breast cancer can devastate women and entire families at first hand. No woman who has relied on the results of modern clinical trials to select a breast sparing procedure following a diagnosis of invasive breast cancer should feel that she has made the wrong choice based on the topics under discussion today.

The principal of breast sparing surgery is based on a set of at least six international studies and a couple that are not yet published, which provide the clear basis for current medical practice. The issue of ipsilateral breast cancer that we've heard, that is a recurrence in the same breast, may, as the facts were presented in earlier testimony, may possibly be Dr. Fisher's view, but I wish to assure the committee that it is more assuredly not my view, and I believe I have made that point clear to the staffers who have been kind enough to speak to me on this point. We certainly consider ipsilateral breast cancer recurrence to be a valid indicator of the process, and in fact, lumpectomy and radiation compares quite favorably in this connection to other available therapeutic approaches.

Before discussing the details of this case, Mr. Chairman, I believe that documents summarizing the NCI's own statistical analysis done through a contractor who is an agent of the National Cancer Institute, that those documents dealing with breast sparing surgery and other treatment approaches have been provided to the committee, and we are also making these reports, the reports that pull out the St. Luc's data widely available, employing computer networks that will make the results as widely available as possible.

In addition, perhaps it is of some interest to the committee that we had outside reviewers and tried to involve statistical experts with a known consumer advocacy position. Dr. Kay Dickerson has reviewed the NCI reports of the statistics excluding the fraudulent data, and she writes, and I'm quoting, "The analyses were clearly presented, and seemed to be properly done."

Before discussing the details of this case, perhaps I could briefly comment on the NSABP. The group has existed for over 35 years as a leading clinical trials component in the breast cancer field. It consists of several thousand doctors at more than 400 sites and is one of 9 clinical trials cooperative groups that conduct large scale clinical studies supported by the National Cancer Institute in the United States and Canada. The NSABP's founder, Dr. Bernard Fisher, constructed the group as a broad based organization of community and academic surgical oncologists whose findings would reflect the ability, the capabilities and the imperfections of practicing physicians in the real world to employ innovative therapies. The NSABP has pioneered and established many principles of breast

cancer treatment that have, in fact, been replicated by other organizations and groups.

Please let me say something that I hope is not misunderstood in testimony before this committee. Today, Dr. Fisher's prior record of scientific preeminence, indeed even the fact that he as a surgeon played a special role in liberating women from having to undergo mastectomies, all of this is irrelevant to reviewing what went wrong and how we should do better.

In June 1990, the NSABP staff detected inconsistent data in the record of a patient previously entered on an NSABP trial in Montreal. This was at L'opital St. Luc. In two site visits of the ensuing 7 months, NSABP became convinced that fraud had taken place, and in February 1991, notified the NCI for the first time. The NCI notified the Office of Scientific Integrity, the precursor of the Office of Research Integrity, which will be represented by my colleague, Dr. Lyle Bevins, and also notified the Food and Drug Administration and the Office of Protection from Research Risks.

Government audits were organized and carried out, and they quickly confirmed the findings of fraud. To be candid, this was not a difficult investigation from my point of view. The investigator, Dr. Roger Poisson, admitted the forgery and falsification of dates and other fabrications in the records of a small number of patients that he entered into NCAB. I use the small number as his point of view, not my point of view. His later justifications for these acts are incomprehensible to us. They remain incomprehensible to us to this day.

OSI—now ORI—undertook a detailed investigation. During such an investigation, ORI generally prefers to have an embargo on public discussions and disclosures. However, Dr. Fisher was asked by both NCI and ORI, orally and in writing, to perform a re-analysis and prepare a publication of the trials affected by the fraud. It is my personal view that had he listened to us or had we been able to force him to listen to us, this hearing would be unnecessary. As early as July, 1991, an SABP assured NCI staff that outcomes were unchanged. In March, 1992, Dr. Fisher presented his re-analyzed data to medical and statistical of OSI, NCI and NIH at a presentation in Bethesda, and concluded there were no changes in the major end points of the affected studies.

NSABP was asked to prepare a manuscript to publish their re-analysis at the conclusion of the misconduct investigation. Neither I nor NCI felt there were any urgent public health hazards or changes in medical practice that would warrant breaking the embargo which ended in April, 1993 with the release of the final ORI report. We are re-assessing the algorithm by which we decide whether an embargo needs to be broken, and this particular kind of faith to an embargo or an adherence to an embargo is unlikely to ever be repeated, at least from my point of view.

The report's findings of fraud were summarized in a number of formats which are not satisfactory and include, of course, the NIH guide in June of 1993. Each issue of the guide is mailed to over 36,000 subscribers and is available on computer networks, but there can be no doubt that ORI and NCI put Dr. Fisher on notice to publish a re-analysis. It is clear, however, that the methods used to announce the results of this misconduct were not adequate, and

we will approach the dissemination of such results working closely with ORI in a more active and visible way in the future.

In February 1994, the NSABP sent NCI a written summary of their re-analysis of clinical trials, including the breast sparing procedure study. Shortly thereafter in March of 1994, accounts in the media generated concerns about the delays in publication and raised the possibility that the practice of medicine might be based on faulty conclusions. I believe it is Dr. Fisher's assertion or the assertion of his staff that he was preparing to publicize these results in June of 1994.

There is cause for reflection and review of actions regarding what the NCAB and NCI did in responding to these issues. First, let us look at NSABP. The NSABP failed to publish its re-analysis, inform its membership of the incident, reassure the public, notify scientific journal editors and other grant supported organizations of the fabrication, public accurate papers that clearly disclose what Dr. Poisson did, and in a larger sense, adhere to NCI's guidelines for management of the group's operation office and quality assurance functions. The NSABP did not respond to constructive criticism by NCI staff.

Unfortunately, the problems of the NSABP have continued. In an NCI on site review of their operations in Pittsburgh toward the end of March of 1994, NCI staff found additional evidence of deficient auditing and reporting practices. The staff found that the NSABP had failed to conduct required audits of its treatment studies in a timely fashion and had failed to transmit to NCI reports of certain audits of its treatment and prevention trials as required.

In the files, we found a report of an additional episode of possible data manipulation involving a patient on a different study at yet a different hospital in Montreal. This finding was initially discovered by the NSABP in September of 1993 but had not been reported to NCI and was, as far as we can tell, being handled as a routine matter subject to an additional follow-up site visit. The NCI staff initiated an emergency site visit to the new institution in question, confirmed a suspicious alteration in an X-ray report, and immediately notified ORI, which is now investigating the matter.

That latest irregularity appears to involve a clinical study, the tamoxifen breast cancer prevention trial that is not completed and therefore is unpublished. I have been informed by ORI that the breast cancer treatment results were not tainted or do not appear to be tainted by this latest irregularity in Montreal.

The NSABP had no explanation for its failure to comply with requests to update and report its audit findings nor for its delay in informing its membership of these problems and promptly submitting its re-analysis for publication. We believe that the primary responsibility for correcting fraudulent work in the literature lies with clinician authors of the original publication. However, as I mentioned earlier, the NCI clearly has responsibilities as well.

Now, let us look at NCI. Despite the requests by NCI and ORI for the group to re-analyze and publish the data and to bring operations into compliance, we failed to compel these actions forcefully and in a timely way. We also did not adequately overcome our reluctance to demand that an independent investigator, who himself was not a respondent in a misconduct case, turn over his data files

in their entirety to have other re-analyze the results. We are trying to learn from this experience to ensure that our response of episodes of fraud in clinical trials is prompt and effective. Thus, recently NCI personnel have taken possession of the computer data files, analyzed and disseminated the results, initiated a government run, on- site audit of clinical research conducted by the group and certain other groups.

In addition, in doing so, NCI has clearly confirmed the principle that the granting agency can and will demand, distribute and disclose a grantee's data in response to pressing public health needs. Fraud will by definition always constitute such a need. We will not tolerate explanations that the data belonged to the grantee. We will never again hesitate to exercise this authority whenever necessary.

Our staff also failed to mobilize after warning signs of delay in clearing up the scientific literature and repairing inadequate compliance with auditing requirements. This may have occurred because of several factors taken alone or in combination, which I believe the committee will wish to note, and these may be: NSABP's proud reputation; the visible status of Dr. Fisher in the scientific community and also as a member of our presidentially appointed National Cancer Advisory Board; a self-consciousness in asserting authority over an independent researcher; or a mistaken belief that somehow the lapses by a senior research group were temporary. We are very sorry that this happened, and we assure you that such errors will not happen again. We have created a new unit, the Clinical Trials Monitoring Branch, to monitor compliance in our cooperative groups, which will implement our rules without fear or favor. We will take swift and uninhibited action in the event of a lack of compliance. A prior record of accomplishments of any level will not be used as a defense against adhering to our regulations. New procedures are in place to report and track audits, and we are initiating a system of NCI-directed site visits to validate the cooperative group audit findings with sites selected at random.

Also, we are reviewing our computer security and password-only entry procedures for the various clinical trials in which a central laboratory runs lab tests on auto analyzers with transfers to a computer database in order to avoid the possibility of the scientific misconduct through a computer hacker could affect centralized computer operations, and we want to address this issue.

We are developing a new internal NCI operations manual for situations involving fraud and scientific misconduct. This manual will be in place within days. The messages also include automatic notification of journals where falsified data had been publish, and in forming other financial sponsors of projects affected by scientific misconduct. Any administrator at the NCI can initiate an automatic series of steps with checklists, enabling NCI as a whole to act decisively and resolutely while at the same time protecting the legitimate interests of all parties. These measures will protect the public health and provide for the recovery of Federal funds. The new branch has begin to review policies and procedures for monitoring trials and plans to revise and amplify the guidelines for every aspect of the process. Dr. Michelle Christian, who is the acting chief of this new branch, is in the hearing room today.

A number of new policies are in force. All site visits will include an individual from outside the cooperative group conducting the audit. All audits will be on site. In addition to any other regular audit and oversight procedures, the NCI, using Federal employees and its own contractors, will conduct special audits of cooperative groups, sites selected at random, to verify the accuracy of cooperative group audits. This will impose an external element of unpredictability and surprise in the auditing and oversight functions.

Accrual of new patients will automatically be suspended for institutions that have not had a site visit with regular 3 year cycles. Audit schedules and reports will be computerized. The NCI is exploring a common on-line computer system to be shared by the groups. The peer review site visit process will be used not only for scientific review, but also to help identify problems in protocol compliance and quality assurance.

The branch will issue a quarterly report to the Executive Committee of the NCI and the NCI components that are doing clinical trials. Grantees that fail to meet our requirements for accuracy, reliability and time limits will be suspended.

We appreciate the need to improve the flow of information on drug toxicities between NCI and the cooperative groups. The early detection of side effects poses special challenges in large community-based clinical trials. As a general rule, in the future, we will try to have the National Cancer Institute in effect actually hold the investigation of a new drug application, what is called the INDA, for studies that we sponsor.

Except under compelling circumstances, I must tell you candidly that this is not always an investigator's or a pharmaceutical company's first choice. But holding the INDA enhances certain types of reporting and additional oversight issues beyond grand management and larger clinical trials. For example, in the tamoxifen randomized trials, NCI did not hold the IND, and therefore would not necessarily have been the very first in line to receive data on new cases of endometrial cancer or other potential complications from tamoxifen. We will try to communicate in novel ways directly with patients on clinical trials. For example, we will tests on a pilot basis an electronic patient information bulletin board to provide patients with the latest communications specific to a given trial. This is to supplement, not replace, our other ways of communicating with patients and consumers, including our cancer information service, cancer facts, and physician data query systems.

What about the current status of the NSABP? The NSABP is an important resource for conducting large scale randomized clinical trials in this country. A number of changes have now been made to strengthen the operation of NSABP. The NCI instructed the granting institution to change the principal investigator, and Dr. Fisher, the leader of the group since its inception, has stepped aside. I do not recall a similar request ever having been made within my historical knowledge of the NCI on a major figure of Dr. Fisher's status. Dr. Ronald Herberman, the director of the Cancer Center at the University of Pittsburgh and a widely respected scientist, has assumed this job on an interim basis. An interim executive officer has been appointed to oversee daily operations. An oversight committee composed of experienced oncologists, breast cancer

specialists, and a consumer advocate has been appointed, and the membership of the group has received information regarding the fraud and operational deficiencies of the group.

It is my personal belief that Dr. Fisher pioneered and established this group prior to even the founding of the national cancer program in its current iteration, and I believe that is a fact that has partially influenced the relationship of who reports to whom. The group has been placed on probation, and it has until the end of June 1994 to initiate programs to bring its auditing and reporting procedures into compliance. Accrual to clinical trials has been temporarily suspended until these deficiencies are correct and a quality auditing system is in place.

The terms of awards of the NSABP grant have been modified to require immediate republication of any trials affected by fraud. Similar grant conditions are being implemented for all of NCI's clinical trials' cooperative groups. Our own NCI run audits of various hospitals and academic centers affiliated with this group continues. We are attempted to recover funds expended at the fraudulent data site. We consider the entire data set from St. Luc's Hospital to be a total loss to the American taxpayers.

We have learned a great deal about the process and pitfalls of dealing with scientific misconduct. We clearly understand the principle that we cannot allow a grantee's formidable reputation, history of prior accomplishments or service in science to stand in the way of prompt, corrective action and oversight. Prior achievements do not render individuals immune to what we must get from them. We cannot and will not ever defer or appear to defer to the timetable of a grantee of whatever preeminence in reporting fraud and fabrication to the public. We have taken steps to make this the explicit policy of the National Cancer Institute.

We hope that the measures outlined above will bolster at least in part the confidence of the Congress, the public, and the medical community in our clinical trials program and will strengthen the operation of our productive clinical trials groups, most of whose members honor careful and honest science and are devastated by episodes of fraud, as are we at the National Cancer Institute.

I thank the Chair for his very generous permission to allow me to go over my time limit. Thank you for providing me this opportunity to testify and present the facts about NCI's role. I would be pleased to answer any questions.

Mr. DINGELL. Thank you, Dr. Broder, for a very helpful statement. Dr. Bivens?

TESTIMONY OF LYLE W. BIVENS

Mr. BIVENS. Mr. Chairman, I'm pleased to have the opportunity to review for the subcommittee the response of the Office of Research Integrity to the allegations of scientific misconduct at St. Luc Hospital. Although the Office of Research Integrity was established in June 1992 and was therefore not involved in the case until that time, I'll attempt to provide briefly the general background of the circumstances leading to ORI's specific role in the case. I'll then describe the nature of our investigation and subsequent activities. I beg your indulgence for some duplication here,

but I think it's important for the record for me to cover background material leading up to our involvement.

In June 1990, the staff of the National Surgical Adjuvant Breast and Bowel Project, a large collaborative clinical trial supported by the National Cancer Institute, discovered discrepancies in two reports of breast cancer surgery involving an individual who was the study subject. This woman was part of the study group from St. Luc Hospital in Montreal, one of the many hospitals participating in the study.

In September 1990, an audit by NSABP staff identified problems with both medical records and documents relating to the informed consent. Dr. Poisson, the principal investigator for the St. Luc component of the study, was informed about these problems in December.

Early in 1991, NSABP reviewed over 100 cases and found five discrepancies in this group. These discrepancies had the effect of making five patients eligible for inclusion in the study who would have not been eligible had the protocol been followed properly.

On February 6, 1991, Dr. Bernard Fisher, the principal investigator for the overall project, suspended accrual of new patients from St. Luc and asked for an explanation of the data discrepancies. Dr. Poisson admitted to alteration of records in a few instances but not to any wrongdoing. On February 14, NCI received notification from Dr. Fisher that irregularities have been found in the data from St. Luc.

On February 22, some 8 months after the initial problems were identified, NCI staff met with Dr. Fisher at Pittsburgh to discuss the findings. At the conclusion of the meeting, NIH's office of scientific integrity was notified by NCI of apparent fabrication and falsification of the data from St. Luc. NCI also notified the Office for Protection from Research Risks and the FDA because of informed consent problems and the fact that some of the questioned data had been filed under an investigational new drug application for tamoxifen.

OSI immediately decided to conduct a direct investigation due to the importance of the NSABP studies in changing standards for medical practice.

On March 1, 1991, OSI opened a formal investigation and directed that all records for the patients be secured and maintained under proper custody. OSI developed a plan to audit a sample of cases entered on NSABP studies from St. Luc hospital. This was a complex task. Three charts were maintained for each case, in patient records, outpatient records and research records and the medical records were in French.

An OSI team along with staff from NCI, NSABP and FDA, made an initial visit to St. Luc Hospital on April 22 to 24, 1992, to review records and interview St. Luc staff. The review team found that 5 to 10 percent of the cases in the sample contained what appeared to be data discrepancies. OSI decided to audit records of all 1,504 patients from St. Luke hospital rather than a sample of cases, as was the original intent. Many of the discrepancies were altered dates of procedures or tests that made patients eligible for inclusion in the research protocol, whereas the correct information would have made them ineligible.

Subsequent review of records was conducted on June 11 to 14 and 25 to 28, and on August 26 to 18. Beginning in September, OSI and NCI evaluated all the information and documents collected during the investigation and compiled a database of falsification and fabrication charges. On February 19 to 21, 1992, OSI revisited St. Luc hospital to confirm details on questionable cases.

An overriding concern from the beginning of this investigation was whether the scientific basis for breast cancer treatment strategies was invalidated by the falsified and fabricated records. NCI and OSI requested early on that NSABP determine whether clinical outcomes were changed. It was requested that NSABP revise the research records with the questionable data excluded. Oral confirmation was provided by NSABP in July, 1991, that outcomes had not changed. At the request of OSI, NSABP presented the reanalyzed data to OSI, NCI, and NIH staff in March 1992. NCI and OSI statisticians were aware that this was a preliminary analysis, and then NSABP was asked to prepare a manuscript to publish the re-analysis by the time the misconduct investigation was completed.

Because the preliminary re-analysis indicated that the basic findings of the study remained valid, OSI concluded that no clinical alert or notice was necessary and, consistent with existing policy, no public information on the case was provided while the investigation was underway.

On April 8, 1992, the OSI again visited St. Luc Hospital, this time with two outside experts to review the cases. From June through November, 1992, the newly established Office of Research Integrity examined all of the evidence, prepared a detailed written report for each case, solicited responses from Dr. Poisson on each case and prepared an overall report which was sent pursuant to our standard procedures to Dr. Poisson for comment in November 1992.

Although Dr. Poisson admitted to altering records early in our investigation, his admissions were very limited and provided in a piecemeal fashion, only after further discrepancies were noted as our audits proceed. It was essential for investigation to uncover the full extent of the misconduct, especially because of the potential clinical significance of the data in question. Therefore, we did not stop our process as soon as Dr. Poisson made a very limited admission.

On January 5, 1993, the NCI sent a letter to Dr. Fisher urging finalization of the manuscript on reanalysis of the published studies. On February 19, 1993, ORI notified Dr. Poisson of our findings and proposed actions, including his debarment from receiving Federal grant or contract funds for years. Copies of our notice and final report were also sent to NIH, St. Luc Hospital, and the University of Pittsburgh. At the same time, I wrote a memorandum to the director of NCI summarizing ORI's recommendations for publication of the reanalyzed studies.

Under a newly establish hearing opportunity for scientists charged with misconduct. Mr. Poisson had 30 days after initial notification to request a hearing. He did not do so, and ORI made its findings final effective March 29 and notified Dr. Poisson of this on April 16.

At about the time that this case was being concluded, ORI had decided that it was in the public interest to provide wide notice of our findings of scientific misconduct. This was a major departure from the practice of our predecessor organizations in which information on cases of confirmed scientific misconduct was released only in response to requests under the Freedom of Information Act. A Federal Register notice was prepared, summarizing all fourteen of the cases of scientific misconduct that had been closed since ORI was established in June 1992, and this notice was published on June 21, 1993.

We also published the identical information in the NIH guide to grants and contracts, a weekly publication sent to more than 30,000 institutions, hospitals, and organizations concerned with NIH research. We described the St. Luc case in the April issue of the ORI newsletter, which is sent to all institutions receiving public health service research funds, as well as to a large number of professional and scientific organizations.

In addition, we issued a brief press release announcing findings in the 14 completed investigations, including the St. Luc investigation. In addition to these releases, we provided the full report of our investigation of St. Luc's hospital in response to six requests under the Freedom of Information Act. Two of these requests were from the media and four were from institutions or individuals.

If, during the course of the investigation, ORI had identified any immediate threat to the scientific basis for breast cancer treatment strategies, we would have taken immediate steps to alert the public and those making treatment decisions based on those studies. There was no such indication, so we adhered to our standard procedure, waiting until the investigation was complete before releasing information.

I believe that ORI properly discharged its responsibilities in this case, conducting a thorough and objective investigation and disseminating the findings widely. However, it is also clear from this case that we can improve our effectiveness when we find misconduct in science. Consequently, we have initiated a number of changes. First, we've instituted a policy to routinely and directly notify journal editors of our findings whenever it appears that corrections or retractions of the scientific literature are warranted.

Second, we're working more closely with the PHS funding agencies in following up our recommendations when misconduct is found or even in cases where there is no misconduct but some remedial action seems required. We established a process whereby we request a report within 45 days of our notifying a PS funding agency, and that certain actions will be taken. This will assure that ORI recommendations are flagged for the PHS, and acted upon in a more effective and coordinated fashion by the Department.

Third, and perhaps most important, based upon the testimony I heard this morning, I believe that ORI should provide a higher visibility press release at the conclusion of any investigation finding misconduct in a clinical trial whether the findings of the trial are invalidated or not. If we had done this in the present case, it might have allayed unnecessary concerns about the validity of the findings of the study. This was our first finding of scientific misconduct in a clinical trial, and our overriding concern was whether or not

there was any immediate need to provide the medical community with some sort of clinical alert that the scientific basis for a treatment strategy might be called into question. However, it is clear that we also need to attend to the concerns and perceptions of those persons most directly affected by the clinical research in question.

I'll be pleased to respond to any questions.

Mr. DINGELL. Thank you very much, Doctor, for your very welcome statement. Dr. Broder, you were speaking on behalf of the NCI. Dr. Varmus, you're here speaking on behalf of the National Institutes.

In order that we have a record which is clear, do you at the National Institutes of Health endorse the statement that was made by Dr. Broder?

Mr. VARMUS. Yes, I do.

Mr. DINGELL. You do. So that essentially becomes the statement of both NCI and the National Institutes of Health and the policies therein, then, as enunciated by Dr. Broder, the policies of NIH. Is that right?

Mr. VARMUS. In principle, of course, the specifics——

Mr. DINGELL. I was comfortable till you said it "in principal", at which point my discomfort level rose.

Mr. VARMUS. I would just make clear that the specific remediation procedures that Dr. Broder was specifying apply to his institute. Other institutes have very similar measures. They may not be identical. I'd want to check them.

Mr. DINGELL. I think you are compelling us to inquire, then, as to the similarities and to get some appreciation. Would you submit to us the remediation procedures at the different institutes so that we can see whether, in fact, they meet your test or Dr. Broder's test?

Mr. VARMUS. We can do so.

Mr. DINGELL. It may be that there are some who are, let's say, not being as vigorous as you and I would like them to be and I think we'd like to have a little look at that.

Mr. VARMUS. May I say, Mr. Chairman, that Wendy Baldwin, the Deputy Director for Extramural Activities, who is sitting behind me, was asked by me a few weeks ago to look at the other institutes' activities. I've been very pleased with what she's found and I think you will agree that they meet the high standards you would like to see in place.

Mr. DINGELL. Thank you, Doctor. Dr. Broder, the representative of the Breast Cancer Coalition complained, and I think properly so, about the lack of information regarding the B-14 treatment trial. Just last Friday, FDA and ICI/Zeneca, the manufacturer of tamoxifen, issued a new warning and label based, in part, on the findings of at least four cancer deaths associated with the administration of tamoxifen in that trial.

The subcommittee has recently obtained from Dr. Fisher a chronology of events related to the deaths of these women and submitted it to NCI for review. What conclusions did NCI draw from your review and the analysis of the timeliness of the disclosures of the deaths of those patients?

Mr. BRODER. Sir, members of your committee were kind enough to give me some information which, in part, we did not have. I was able to review them last night.

It is my professional judgment that we should have received information on certain facts and, particularly, if it would be possible, to have information on endometrial cancer early in 1992, possibly earlier, and that information was not provided to us until substantially later than that.

This speaks to the issue of us wanting to hold the IND for such studies, which we did not have. But there was no information provided and I believe that early in 1992, certain information about an endometrial cancer death could have been provided to us.

Mr. DINGELL. So it would be fair to say that one of the deaths should have been understood and reported in early 1992. Is that fair?

Mr. BRODER. That's correct. I'm trying to be fair and physicians may have their own interpretation. This particular patient was initially signed out as a pulmonary embolism, or at least that's the facts as I know them. Since the diagnosis had pulmonary embolism in it as the cause of death, I believe there was some legitimate basis for not making a decision. But I personally believe 1992 would be fair.

Mr. DINGELL. Without objection, we'll put the chronology of that in the record.

[The information follows:]

STUDY NUMBER	DATE OF ENDOMETRIAL CANCER	FIRST SUMMARY FILE CONTAINING ENDO. CANCER (DATE APPROVED)	FIRST NOTIFICATION TO ZENECA	DATE OF DEATH	FIRST SUMMARY FILE CONTAINING DEATH INFO. (DATE APPROVED)	FIRST NOTIFICATION OF DEATH SENT TO ZENECA
14-0134-123	09-20-91	03/92 (06-17-92)	02-01-93			
14-3137-905	9-13-90	12/90 (03-04-91)	01-30-92 *			
14-0318-137	11-18-82	12/92 (05-05-93)	--			
14-0627-053	04-09-91	12/91 (02-19-92)	02-01-93	03-06-92	09/92 (01-06-93)	02-01-93
14-0760-078	01-12-90	06/90 (09-04-90)	01-10-91			
14-0984-026	11-22-91	03/92 (06-29-92)	09-30-92	04-22-92	03/93 (06-29-93)	--
14-1073-407	02-16-93	03/93 (06-29-93)	--			
14-1270-097	08-04-86	07/87 (N.A.)	01-22-88			
14-2182-039	02-06-89	06/89 (09-14-89)	10-16-90			
14-2444-055	01-09-92	03/92 (06-17-92)	02-01-93	07-26-93	09/93 (PENDING)	--
14-3251-444	03-06-91	03/91 (05-30-91)	01-30-92			
14-4211-014	04-18-90	09/90 (11-21-90)	01-10-91			
14-4675-014	09-30-92	03/93 (06-29-93)	--	10-09-92	03/93 (06-29-93)	--
14-4862-629	05-01-93	09/90 (11-21-90)	01-10-91			
14-2915-884	03-09-93	06/93 (10-08-93)	--			
14-3461-873	08-06-93	09/93 (PENDING)	--			
14-2882-866	09-30-86	01/87 (N.A.)	01-22-88	10-15-91	06/93 (10-08-93)	--
14-2236-444	06-13-88	09/88 (01-26-89)	01-30-89			
14-3877-196	03-01-89	12/91 (02-19-92)	02-01-93	06-25-91	09/91 (11-22-91)	01-30-92
14-4726-184	12-15-89	03/90 (07-06-90)	01-10-91			
14-5546-065	09-29-89	12/92 05-05-93)	--			
14-5550-097	11-13-90	06/91 (08-27-91)	01-30-92			
14-5596-043	02-06-92	06/92 (10-07-92)	02-01-93 **			
14-5909-864	05-28-92	12/92 (05-05-93)	--			
14-4475-406	03-05-93	06/93 (10-08-93)	--			

* FIRST SECOND PRIMARY SITE IS LG. INTESTINE

** FIRST SECOND PRIMARY SITE IS CONNECTIVE TISSUE

Mr. DINGELL. Now, is it fair to say that the NCI and the manufacturers should be notified in 1993 about a second death?

Mr. BRODER. That's fair.

Mr. DINGELL. The notification of the third death should have occurred by at least January 1993, isn't that so?

Mr. BRODER. I believe that that's fair.

Mr. DINGELL. So you have three and then the fourth death, there should have been a notification by at least August of 1993, isn't that right?

Mr. BRODER. Sir, I believe that's correct, but if that specific——

Mr. DINGELL. I'm not going to hold you to something. You consider yourself free to respond to that question later, as the need might occur.

Mr. BRODER. Yes. Recognizing that there might be a minor deviation from that specific date. But I do take your point and I believe it's substantively correct.

Mr. DINGELL. When were you notified, Doctor?

Mr. BRODER. Sir, we received our notification through an NSABP meeting that was held in October—toward the end of October of 1993.

Mr. DINGELL. Substantially later than the time that you should have been notified.

Mr. BRODER. You are correct.

Mr. DINGELL. Doctor, is it your testimony that the American public should be informed about the deaths associated with tamoxifen, as well as increased cancers associated with tamoxifen in 1992, not 1994?

Mr. BRODER. I believe that an appropriate notification should have started early in 1992.

Mr. DINGELL. Here we have a bunch of women who have participated in a test. They were advised of certain matters in connection with this to achieve their informed consent. The testimony so far indicates that they may not have been properly and adequately advised to give their full and adequate consent based on a fair exposition of the facts and the risks and the data available to the examiners.

Is that a fair statement?

Mr. BRODER. I believe it is fair. But if you will permit, the situation has a complexity in that the very first informed consent did disclose to patients the possibility of lethal outcomes. They were related to embolic, thrombophlebitic and cardiovascular. So the patients were on notice that death was a possibility.

The patients were also on notice that endometrial cancer was a possibility. But you are quite right and I believe your point is well taken that the issue of endometrial cancer, which should have been brought up to current state, was not provided.

Mr. DINGELL. The risk with regard to uterine cancer was either not stated or was significantly understated.

Mr. BRODER. The risk of death from uterine cancer most assuredly was not properly and adequately provided.

Mr. DINGELL. As a matter of fact, was there any information at all with regard to possible fatalities resulting from this?

Mr. BRODER. Death to certain——

Mr. DINGELL. From uterine cancer.

Mr. BRODER. From uterine cancer, no. But death due to other causes was—the patients were put on notice that there was a possibility of a lethal outcome from exposure to tamoxifen.

Mr. DINGELL. Is there any requirement now in the protocols or the rules and regulations of either NCI or NIH that would require women to be properly notified in connection with the risks?

Mr. BRODER. What we are doing now is that we are reexamining and will, as a condition of a grant, require the same kind of notification that the grantee would owe to the IND holder. We want to be in the information loop immediately, not as an afterthought. We are prepared to not fund proposals where that is not possible.

In a community-based study, which is far flung and, by definition, has a number of sites at multiple areas and also has central pathology services and other things that need to be done, one has to accept a certain amount of delay. Also, there is a need to make sure that if an alarm is sounded, that it is based on very valid information so that the meaning of the alarm would be preserved.

With all of that, I think that our processes need to be improved and we are taking steps to make sure that the grantee understands that. We will also strongly discourage either the private companies or the individual grantees from holding the IND, which, in effect, was the case here for the tamoxifen studies.

Mr. DINGELL. Doesn't it—I'm sorry. Dr. Varmus, go ahead.

Mr. VARMUS. It is, of course, NIH policy that all of our consent forms reveal all of the relevant information that would constitute risk to patients enrolled in these studies. We ask our Office of Protection from Research Risks and the Institutional Review Boards, which include members of the public, often consumers who are involved in these studies, to be sure that the consent forms do adequately describe all of the known risks.

Mr. DINGELL. Have all of the women who were put at risk by the failure to adequately disclose the risk levels with regard to uterine cancer or other perils been informed of the new level of risk or the level of risk as we now know it?

Mr. BRODER. I'd like to ask Dr. Friedman to comment on where we are with that process.

Mr. DINGELL. They either had been advised or they had not been advised. We can get, I think, a fairly simple yes or no answer.

Mr. BRODER. In that case, the answer is no.

Mr. DINGELL. The answer is no.

Mr. BRODER. The process in large, far-flung, community-based studies requires several steps. We could theoretically provide notice of some type. A local institutional review board not responding to the government must approve and endorse any changes in informed consents.

We do try to make the information as publicly available as we can, but I cannot assure you that every single woman has signed a new informed consent.

Mr. DINGELL. I'm trying to understand. We have many questions here, one of which is the simple moral question. Shouldn't these women be informed of the fact that they have been put at additional risk which was not disclosed to them at the time they agreed to participate in the study?

Mr. BRODER. Yes. And that process is going on now and will be completed. If your question is will every single woman be notified, the answer is yes.

Mr. DINGELL. When will that occur? Because they are now all at additional risk with regard to uterine cancer, some also with regard to blood pressure and possibly other matters. When will they receive notice?

Mr. VARMUS. Mr. Chairman, all of the 309 sites of the tamoxifen prevention study have been informed of the recommendations to change the consent forms to be in accord with the newly available evidence. Now, of course, it is the responsibility of those who are in charge of the study at each of those sites to respond and to inform each of the patients.

The NCI itself, of course, can't inform the patients directly. We're informing them through the several hundred sites that are participating in this multi-institutional study.

Mr. DINGELL. Have you told me that all of the women have been informed or just that the sites have been informed?

Mr. VARMUS. All of the sites have been informed and we hope, we trust, and we will enforce the——

Mr. DINGELL. One of the great charities or one of the three great virtues. But this committee has always, in dealing with matters of this kind, sought greater response from the government than simply trust in the great virtues.

I'm curious. How are we to say that the sites have informed the women? We cannot say so, can we?

Mr. BRODER. Mr. Dingell, you are quite right to raise this issue. The trial is currently suspended. We have taken our process of how one informs women of new and evolving side effects to the Office of Protection from Research Risks, which advises us in that process.

Perhaps you might also wish to take into account the fact that in any study there will be an ongoing process of new risks, some of them acute, some of them longstanding, and some of them chronic. There's always going to be an updating process. So this is not the only time. We're going to have to continuously modify our informed consent.

The Office of Protection from Research Risks advised us that upon their evaluation, this process did not require an immediate call-back notification, but could be done in the normal cycle in which women would come back to clinic. We, however, have chosen not to take that option and we will be calling women back.

In addition, we will have a process to ensure that sites have notified all women before that site can re-accrue women in the process when the current suspension is over.

Mr. DINGELL. I hear a goodly number of things, but we have established clearly that we cannot say that the women have been notified.

Mr. BRODER. I cannot tell you that every single woman has been notified.

Mr. DINGELL. We've also come to the conclusion, and I think you concur in this, Dr. Varmus, that there is a moral requirement that the women who participated in this study should be given correct information about new risks which have come to light since the

time that the study was initiated and since they were advised of the level of risk. Is that not so?

Mr. VARMUS. Yes, I agree with that.

Mr. DINGELL. And we can establish that we do not know, but we hope that the women have been informed by the sites. Now, we can observe fairly that the women involved in the test are probably still taking the drug, can we not?

Mr. VARMUS. Mr. Chairman, we will be in touch with every one of those sites to ensure that every woman who is enrolled at those sites has received the information.

Mr. DINGELL. That has not yet occurred.

Mr. VARMUS. That's correct.

Mr. DINGELL. We also have a modest little problem in the fact that the women should be informed so that they can know what the new level of risk might be. We also had the additional problem that there is no requirement in the rules or regulations of NIH that the women do receive notification of changes in the level of risk to them from this particular test program of which they have become a part. Is that not so?

In other words, there is no requirement in the program that the women be warned of changes in risk as they occur to them or in incorrect representations to them of the level of risks which were made early on to induce their participating the program.

Dr. Chabner, do you want to comment on that?

Mr. CHABNER. Yes. There is an absolute responsibility to notify participants.

Mr. DINGELL. You agree there's a responsibility, but what is there in the regulations?

Mr. CHABNER. Yes. The IND holder must notify participants in a trial.

Mr. DINGELL. You can, but this has not been done and it is not in the regulations at NIH to require the women to be informed, is it? Yes or no?

Mr. CHABNER. I'm not sure.

Mr. DINGELL. Well, that's a good answer. It tells me that there is no requirement at NIH.

Mr. CHABNER. I know it's a requirement for the IND holder.

Mr. DINGELL. Maybe Dr. Friedman or Dr. Broder or Dr. Varmus can tell.

Mr. BRODER. Mr. Dingell, I'll shortcircuit the issue. I will just speak for the NCI. There is a requirement.

Mr. DINGELL. There is a requirement?

Mr. BRODER. I'm saying there is a requirement.

Mr. DINGELL. Has that requirement, then, been honored here?

Mr. BRODER. It has not been honored from the point of as we speak today.

Mr. DINGELL. But as we speak today, women are taking tamoxifen. And as we speak today, women are not being informed of the level of risk that they confront. As we speak today, women are not able to go to their own doctor and say ,"Doctor, should I continue in this research program with a potentially increased level of risk." Nor are they being informed that they can have their own doctors inquire and to monitor with greater care into their level of safety.

Mr. BRODER. If I could say, the methods that we—we cannot, under current operating rules, command an institution to adopt our informed consents. But we will reexplore that issue even. What we are trying to do is—the process involves sending out changes. One of the points I would like to stress is that there will be many changes. There are new things that one learns in any study.

So we have a process. This will not be the last time we will change this informed consent or others. What we are trying to do in the interim is notify women in a number of ways, notify women through the cancer information service, which women can call, notify them through our electronic data boards. A letter from Zeneca is in our PDQ and cancer facts system.

In other words, we are doing what we can to get the word out. We will have rules in place so that accrual cannot start and institutions will need to document for us that all women have been informed. But you are right that the process has a certain delay element in it.

Mr. DINGELL. But here you have the good Dr. Fisher, the University of Pittsburgh, all the grant recipients, all the folks who are participating in the study, and you have imposed no requirements on them, as the record stands at this particular time, requiring them to report to the participants in the study of new information relative to risk, nor of increased risk which has come to your attention.

You're doing all this wonderful work and I appreciate that, but you're not imposing any requirement on the dear University of Pittsburgh or the good Dr. Fisher to get this information to people who may potentially be put at risk by the changes in the circumstances, by the new information, and by the failure to adequately warn them back in 1992.

Is that a fair statement or not?

Mr. CHABNER. Congressman, the University of Pittsburgh, Dr. Fisher, holds the IND in this trial. They have a legal obligation to notify participants in their trial. That is an obligation.

Mr. DINGELL. Have they done that?

Mr. CHABNER. They've been instructed to do it. Whether they've done it or not——

Mr. DINGELL. They seem to be somewhat deficient in following up on instructions, according to what we've gotten today.

Mr. BRODER. We take your point.

Mr. DINGELL. Remember, the IND, that's the investigation on the new drug, is that right? That is not an NIH requirement.

Mr. BRODER. That's correct.

Mr. DINGELL. That is a Food and Drug requirement, right?

Mr. BRODER. Yes. But as a requirement to get the grant, they must have the IND.

Mr. DINGELL. Pardon?

Mr. BRODER. It is our requirement, in order to do the study, they must have an valid IND. So if their IND is revoked or improperly being performed, then the study must stop.

Mr. DINGELL. It probably is too much to say they've been snapping their finger under your nose, but certainly their behavior has been less than the requirements that you would impose on them

in terms of good moral behavior or in terms of seeing to it that the experiment is conducted in a sound scientific fashion.

Mr. BRODER. They don't respond to constructive criticism.

Mr. DINGELL. Well, we're going to help. We think that now we maybe ought to have the University of Pittsburgh before us to discuss these things. Maybe we might have you and Dr. Varmus back, and maybe Dr. Chabner and Dr. Friedman and maybe even Dr. Bivens, because we sense that matters are not being handled in a way which makes this information fully available to the women who have been involved in the test.

The women are already in the treatment trial. Many have taken the drug for as long as 10 years.

Mr. BRODER. For therapy of breast cancer, that's correct. They take it for multiple years.

Mr. DINGELL. And some are taking it as a preventative. Now, there appears to be strong evidence that, in point of fact, it's not a good preventative and there also appears to be some significant evidence that it imposes additional risk stemming from potential other perils; i.e., uterine cancer and blood pressure phenomena.

Mr. BRODER. May I respond to that?

Mr. DINGELL. But neither you nor Dr. Varmus are able to tell us that this information has been made available to the women who are involved in the study. We are trusting the Food and Drug Administration, which, not infrequently, we have before this committee to discuss some of their shortcomings.

Mr. BRODER. Mr. Dingell, I take your point. Perhaps, with your permission, I'd like to ask—well, Dr. Ford has not been sworn in. I will certainly provide to you for the record the steps that we have taken.

But if you will permit me a very brief interval. You made a statement which I would argue is still open to some discussion. We understand, respect and fear breast cancer. It is an invasive disease and a woman who develops breast cancer has, in spite of all the best things that we have to offer and we have had improvements, but on average, a woman who develops breast cancer has approximately a 50 percent chance of dying of her disease.

I come to you to this table with an appreciation of the formidable quality that breast cancer has. We do not have any immediate preventions to offer women who are at high risk. Some women, under 50 and over 50, have risk factors which we can identify that impose an enormous burden of the possibility of breast cancer for them and they don't have any options.

What we are saying by the tamoxifen study is that certain women who have high risk of breast cancer can possibly—we will possibly learn whether tamoxifen could be a preventative for those women. We have certain things, like hormonal replacement therapy, which is available in this country in any drug store by a prescription, which causes certain benefits to women who are postmenopausal, but which is associated with a comparable endometrial cancer risk, and it's never been the subject of a clinical trial.

All we are saying is that we understand the problems, but tamoxifen has been one of the few things in the scientific literature

which has a proven and multiply replicated reduction of contralateral breast cancer in women who already have had——

Mr. DINGELL. Doctor, we do not talk about it as a useful treatment device for breast cancer.

Mr. BRODER. Even for prevention.

Mr. DINGELL. I do not quarrel about that.

Mr. BRODER. What I'm talking about is it is—what we have learned is that women who have breast cancer have a separate and independent risk not only of recurrence, which is one problem and is the most often thing we're talking about, but they have an independent risk of developing a new breast cancer in the opposite breast.

Tamoxifen has been shown to reduce that in several studies by a substantial amount. Therefore, it also possibly may have certain effects for myocardial infarctions and so on. Women who already have breast cancer who have received tamoxifen have fewer heart attack rates than the control group.

We are not saying that tamoxifen should be used. We ask for it not to be used for prevention. What we are saying is for women who are at risk, we ask for the opportunity to do a clinical trial so that we can inform you and the public as to whether this is an option. That's all we are saying.

Mr. DINGELL. Let us lay this matter to rest. I am not quarreling with the fact that you're performing the test. I am trying to address the reporting, the disclosure and the information which is given to the women who are involved in the particular test.

We've talked here about reports with regard to treatment and with regard to prevention. But I'm trying to find out the reports that you have received in each instance and the reports that the women who are involved in these programs are receiving. I sense that they may be getting certain reports in connection with the treatment program, but they may not be getting it in connection with the prevention tests which are going on.

Now, am I fair in that inference or not?

Mr. BRODER. Yes, you are. You are fair and within 24 hours we will give you a report of the status of what our information flow has been.

Mr. DINGELL. That would be very helpful. My time has expired and I want to recognize my good friend and I'm going to apologize to him right now, but there's a question that we have not gotten an answer on. We do not now know whether the women have received the necessary notification of either the new risks, the new circumstances, or the failure to adequately inform them.

We do not know yet whether or not you have in your rules and regulations and in the protocols the requirement that kind of information be made available. We do not know whether that kind of information has, in fact, been made available and whether there is a policy change needed at NIH to see to it that this notification goes forward to the people who have been put at additional risk because of the kind of situation we find in the tamoxifen tests.

Can you tell us whether or not you have requirements in the protocol, either at NIH generally or at NCI, which requires that this new information be made available to the persons who were involved as it comes available?

The problem we have here is women are at risk. Women are subject to potentially higher levels of risk of cancer, uterine cancer, in connection with it. We also want to know whether they are able, then, to monitor their own affairs more fully and carefully because they have the risk that they can take to their own doctors or that can be made available to the researchers who might be working with them at the different sites.

Can you address those questions, please?

Mr. VARMUS. Mr. Chairman, let me see if I can help with this. Under the Office of Protection from Research Risks, we have rules that dictate that information that concerns adverse outcomes or adverse effects of instruments used in clinical trials or prevention trials be communicated to the institutional review boards at the sites at which these studies are being conducted.

Mr. DINGELL. That's to the people at the site.

Mr. VARMUS. Let me finish, please. At those sites are found the names and addresses of study participants. We do not have at NIH the names and addresses of participants.

Mr. DINGELL. I'm not critical of NIH with regard to your inability to notify these people. I am trying to find out whether you have a situation which does require the necessary notification.

Mr. VARMUS. It is a regulation that all patients in the study be informed through the institutional review boards. You're raising a legitimate question of whether we should have tougher rules to follow-up on the notification process. You can rest assured that we will be looking into that very vigorously.

Mr. BRODER. I'd like to second that, because I want to assure you that we take your concerns and criticisms very seriously and to heart. I believe they are valid. We will look to see whether there is a structural problem that we can repair. We will also explore, although I cannot promise you today, whether at least the NCI has some right of direct access to patients. I believe that we will probably be told that we have limited access.

Mr. DINGELL. I think it would be useful if you had direct access, but I think it's even more useful if you could simply require that the patients do be informed.

Mr. BRODER. That is done.

Mr. VARMUS. We do require that.

Mr. BRODER. That is required.

Mr. VARMUS. But you're asking whether I know that all the patients have been informed and I cannot say that I know that.

Mr. BRODER. Also, we have limited rights of asking a grantee to provide names and addresses, but we will certainly try to review that, as well.

Mr. DINGELL. The deaths should also have been reported in 1992 before any of the patients entered the prevention study, should they not?

Mr. BRODER. That's correct.

Mr. DINGELL. That was not done.

Mr. BRODER. That was not done. As far as I can tell, it was not done even to the FDA.

Mr. DINGELL. Can you tell us why?

Mr. BRODER. I would have to speak for Dr. Fisher and I would prefer not to do that.

Mr. DINGELL. Well, it might be a little bit difficult. As the record shows, we have invited Dr. Fisher to appear here and he has indicated that his health prevents him from being with us. We perhaps will be affording him another opportunity, but as I have indicated, we are going to be asking the university to come forward.

Mr. BRODER. I hope his health improves.

Mr. DINGELL. Pardon?

Mr. BRODER. I hope his health improves.

Mr. DINGELL. I do, too. At least enough that he can appear here before us. Well, the Chair has used more time than I am entitled to. The Chair recognizes the gentleman from Colorado, Mr. Schaefer.

Mr. SCHAEFER. Dr. Broder, the NCI issued a statement on March 14 of 1994 that I would want to read for the record. I'm sure you're familiar with it. Its headline is "National Cancer Institute's Statement on Breast Cancer Treatment Studies."

The original conclusion reads as follows. "Following evidence that fraudulent data has been submitted as part of large breast cancer treatment group trials, the scientists overseeing the trials and staff of the National Cancer Institute reanalyzed the data. The re-analyzation was done without any of the data supplied by the investigator accused of fraud and that reanalysis using data exclusively from other institutions participating in the group reaffirmed original results."

Was this a true statement when it was issued?

Mr. BRODER. I believe it was substantively correct. There are many issues about what the word "reanalysis" meant. But there was in hand at that point a report from the NSABP which had certain issues of discussion, but which substantively confirmed the end points and did remove the fraudulent data site.

Mr. SCHAEFER. Did the NCI analyze this data?

Mr. BRODER. The NCI did not analyze the data. The people overseeing the study that I believe you read were the people from the NSABP, the principal investigator. The NCI analyzed the data from the standpoint that our statistician, a government statistician who critically reviewed the report, made suggestions that were transmitted back to the NSABP, but, in fact, did feel that the substantive issues were valid, that the substantive end points were valid.

Mr. SCHAEFER. But NCI was forced to retract the statement after it was released. Is that correct?

Mr. BRODER. It became a definitional term about the word "analyze." I believe that people of goodwill can use that term in multiple ways. We understand that term had a special meaning and when individuals meant the term "reanalyze", they wanted us to be the individuals to reanalyze it.

I'm sorry for the confusion. It will not happen again.

Mr. SCHAEFER. What about the ordinary people who were involved in reading it? Did they understand this stuff?

Mr. BRODER. The word "analysis" is open to multiple interpretations. One can analyze a scientific experiment or analyze somebody's argument or analyze a problem without necessarily doing the firsthand work oneself. One looks at the work product and then analyzes it. That was the use of that term.

We're sorry if there is confusion on that point, but we do have our own analyses which have been provided to the committee. So any doubt or ambiguity on this point has now been laid to rest.

Mr. SCHAEFER. Let me ask you this question. How many people received this erroneous statement?

Mr. BRODER. Sir, with respect, this is open to different interpretations. If you believe the statement was erroneous, I will accept your point. But I believe the term "analyze" is open to multiple interpretations.

Mr. SCHAEFER. But you still had to retract it and then reanalyze it, didn't you?

Mr. BRODER. But we have the reanalysis, sir. It's been provided. Our own analysis of the relevant studies has been provided to the committee. It is on Internet, it is on our electronic databases. It has been sent to members of the National Cancer Advisory Board. It's been sent to Kay Dickerson, it's been sent to Fran Visco and so on.

These are our own analyses, not the NSABP. We have distributed this and we are sorry that there may have——

Mr. SCHAEFER. This is an updated analysis now.

Mr. BRODER. No. It is our work. We asked for and demanded the original computer data files, something which is done extremely rarely. It will be more common in the future. But we asked for and were provided the original data files. We are also doing chart audits, which is different from the computer data files. But those documents have been provided. I can provide them to you now, if you will permit me to put them into the record. I have them with me.

Mr. DINGELL. Without objection, so ordered.

[The documents referred to are retained in subcommittee files.]

Mr. BRODER. With the Chair's permission, I will provide you with the documents as they are being distributed.

Mr. SCHAEFER. I really want to get down to this point. The first statement was issued. It was retracted, or it was redone or reanalyzed. What was it? There was a difference, right? So, therefore, people read the first statement and how did they——

Mr. BRODER. And they're true and they say different aspects of it. In the early portion of February, we received an NSABP report which analyzed, statistically analyzed the end points of the various studies affected by the fraudulent data site, with and without the data site from the fraudulent site in the report.

With the Chair's and the committee's indulgence, I have to introduce a term. They analyzed it by intent to treat, which is a valid way, but did create some confusion. I can define that term now or I can define it to you for the record.

But it does provide a valid way of analyzing material. That was reviewed by our in-house staff and it was reviewed by Dr. Simon, who raised certain criticisms, constructive criticisms that were provided. But the conclusion was that the Poisson data removal did not change any of the major end points. In fact, the studies basically, in most of the major things that we discussed, were the same.

We have, in addition to that, demanded the original computer data files and have run with our own agents a reanalysis independently down here in Bethesda. Those reports are with me today and I will be glad to submit them to you for the record. They have al-

ready been circulated. They are, as we speak, being circulated. They are on Internet. They are available by our—anyone who has a computer service can download this through our PDQ system and so on.

So what I'm trying to say to you is that this process has more closure than perhaps—it's called the EMMES analysis because this is a private, highly sophisticated, statistical firm that's a contractor that reports to us. They did everything from the computer data files.

We also are auditing the various sites with our own government workers or contractors that report to us. Dr. Friedman is prepared to provide you with the audit summaries as to where we are today.

So I apologize if the term "analyze" had some confusion, but to those of us in the scientific community, the word "analysis" or "analyze" has multiple interpretations. But all interpretations of that term have been resolved as we speak today.

Mr. SCHAEFER. Let me ask you this question. Did the reanalysis review all the points in the same manner as the original analysis?

Mr. BRODER. It did it both as to the original analysis, but because we had possession of the computer data file, we were able to ask and clarify questions that individuals have raised; for example, the ipsolateral breast cancer story we could address and we could do certain kinds of analyses that were not even in the original publications.

So the answer is, yes, we did and we did more. So there is a value-added function in looking at the reports that we have and the reader will be able to get more information.

We also have a copy of the New England Journal of Medicine submittal which we compelled Dr. Fisher to submit. I have provided a copy of that New England Journal paper to the committee and would be prepared to distribute it to any members of the committee who wish to have it. If the committee advises us to, we will make the New England Journal submittal public, as well.

Mr. SCHAEFER. Who was responsible for releasing this statement in the first place?

Mr. BRODER. This was probably coordinated through our Office of Cancer Communication. I will accept responsibility for this and any other matters that the committee feels needs to be accounted.

Mr. SCHAEFER. We did a re-analysis and I just want to say that for the common lay person out there, who may not understand scientific terms, that we would do well in the future to make sure that whatever is conveyed to these individuals, is not going way over their heads. They'll know exactly what was talked about.

Mr. BRODER. Sir, these will be the documents that will be submitted so that they can be identified. These are the documents that we have done. I have with me here a copy of Dr. Fisher's New England Journal of Medicine paper.

What I would like to advise the committee is that we have additional analyses in our preparations, looking at different data points and different ways of looking at the data, that actually are not even considered in this paper, Dr. Fisher's paper. But the bottom line is that we have looked at all of the end points that we know how to look at and including some that he has not published.

Mr. SCHAEFER. Would you then say that the three ladies that we had here prior to this panel, that they would take those and could understand them?

Mr. BRODER. I believe so. I believe the panel was composed of extremely intelligent women who have asked good questions and who understand the facts and are among the most tragic aspects of this issue. Basically, we need to understand at the National Cancer Institute that we report to the first panel and not to Dr. Fisher.

Mr. SCHAEFER. Mr. Chairman, I'm over my time here. I have a couple other questions.

Mr. DINGELL. The Chair will recognize you further.

Mr. SCHAEFER. Dr. Friedman, you were responsible for overseeing and monitoring the reports that came in from the University of Pittsburgh, is that correct?

Mr. FRIEDMAN. Yes, sir.

Mr. SCHAEFER. How many people were assigned to this specific oversight?

Mr. FRIEDMAN. There were two people at that time in the auditing section. Neither one was devoted specifically to the University of Pittsburgh. Both had responsibility for auditing and quality assurance oversight.

Mr. SCHAEFER. Is this an adequate number to correctly do it?

Mr. FRIEDMAN. I think the problem was not so much the numbers as the procedures and the ability that we exercised in having what Dr. Broder has described as constructive criticism actually translated into meaningful action.

Mr. SCHAEFER. How can we assure that reports now coming from the University of Pittsburgh are being adequately monitored? Are you investigating whether you're going to use more people or not?

Mr. FRIEDMAN. Sir, there are a number of answers to that question and I will be happy to give you the various aspects of it and then ask Dr. Broder or Dr. Chabner to supplement anything that I have left out.

First of all, the entire way in which business is conducted, research business and quality assurance business at the University of Pittsburgh and the National Surgical Adjunct Program, has been changed. The laxness, the imprecision which characterized some of their administrative activities in the past no longer is allowed to exist today.

So that they must provide to us and have provided to us a complete auditing schedule. They understand what their requirements are for reporting things to us in a timely way. By that, I mean they must report to us within 24 hours after an audit is conducted. We must have within 6 weeks a written report of that audit.

Mr. SCHAEFER. When was all this changed?

Mr. FRIEDMAN. Sir, these were new—when the University of Pittsburgh and this group were put on probation at the very end of March, a whole series of instructions were provided to them and those are the features that I'm speaking about, sir.

Mr. SCHAEFER. So we had to have an issue like this come out before you were moving to do new things on adequately monitoring this information.

Mr. FRIEDMAN. Sir, the numerous times that we contacted——

Mr. SCHAEFER. We're dealing with a lot of women's lives here.

Mr. FRIEDMAN. I'm sorry, sir. I didn't hear you.

Mr. SCHAEFER. We're dealing with a lot of women's lives in this country.

Mr. FRIEDMAN. The subject is enormously important. The quality of these data, the trust with which the public holds these data are terribly important. Our ability to compel Dr. Fisher, our ability to institute changes that we had recommended did not occur until very recently.

Mr. SCHAEFER. So you had recommended these changes prior to these statements and the studies being issued?

Mr. FRIEDMAN. Yes, sir, we had.

Mr. SCHAEFER. And it was stonewalled. In other words, nothing was done.

Mr. BRODER. I believe the correct answer is that Dr. Fisher, maybe not directly, but, in effect, told us by implication that he's been doing clinical trials a long time, perhaps before we were out of school. He knows what to do. He's been doing things since the late 1950's and he knows how to get the job done.

No one will ever tell us that again. We will do what we have to do. Our staff understands the mission. They understand what we need to do. I believe that Dr. Fisher has made a number of accomplishments and I believe his accomplishments have benefited women to an extremely high degree. That's not the issue here today.

The issue here is that no one is above our rules and we will see to it.

Mr. SCHAEFER. Well, I think that's something that the chairman and I are very pleased to hear. If I might ask one more question, Mr. Chairman.

Mr. DINGELL. The gentleman continues to be recognized.

Mr. SCHAEFER. Dr. Broder, did any officials at NCI notify the editor of the New England Journal of Medicine that the St. Luc data was in doubt?

Mr. BRODER. No, they did not, until very recently.

Mr. SCHAEFER. Why weren't scientific journals notified?

Mr. BRODER. Because it was the mistaken belief that the primary obligation should be with the person who authored the words. I still hold to that principle. The person who authors a paper has the primary duty to retract and correct that paper, irrespective of what a government agency does.

So even though we are changing and I will provide you with a different point of view, I still think that responsibility should not be lost sight of. The primary duty for correcting a paper lies with the primary investigator who wrote the original paper.

The belief, I believe, was that Dr. Fisher was extremely preeminent, extremely experienced, knew what he was doing. In addition, there was some inhibition and self-consciousness about ordering him to do anything.

The other issue is that it would have been best for all parties had there been a simultaneous process in which Dr. Fisher and our group cooperated in revealing all of the facts as promptly as possible. It becomes difficult and awkward for the NCI to act alone without the investigator cooperating with us.

However, that will not happen again. We will have in place a policy in which these things occur promptly, even possibly and likely, in fact, in a clinical trial before the ORI investigation is over, and we have proven that. You have a press release today, I understand from Dr. Bivens.

Mr. SCHAEFER. What is the press release? What does it deal with?

Mr. BRODER. Dr. Bivens?

Mr. SCHAEFER. You're saying you're going to change the way you're doing——

Mr. BRODER. No, no, no. It's a substantive press release.

Mr. BIVENS. I don't know if it has been released or not.

Mr. BRODER. The press release is being released today on a second case of fraud at——

Mr. SCHAEFER. A second case.

Mr. BRODER. Yes, at another hospital in Montreal.

Mr. SCHAEFER. Dealing with breast cancer?

Mr. BRODER. That's correct.

Mr. SCHAEFER. Or something else?

Mr. BRODER. Dealing with breast cancer.

Mr. SCHAEFER. Well, just briefly tell me and Mr. Chairman here what this press release says.

Mr. BRODER. I believe the facts have been provided to the committee.

Mr. SCHAEFER. Do we have that?

Mr. DINGELL. There was a comment, I believe, in Dr. Broder's prepared testimony on this particular matter.

Mr. BRODER. I addressed this point in my opening statement.

Mr. VARMUS. This matter has been reported in the press previously. There have been allegations of irregularities or there have been irregularities detected in recordkeeping in St. Mary's Hospital in Montreal.

Mr. DINGELL. Did that also involve Dr. Poisson?

Mr. VARMUS. No, it did not.

Mr. DINGELL. A different doctor.

Mr. VARMUS. It was a different case. It was a case that was most recently described in the press after the NCI visited the NSABP Center in Pittsburgh. The case was reported to the Office of Research Integrity and that office is investigating the nature of the irregularities and determining whether or not they constitute scientific misconduct.

Mr. BRODER. But Dr. Fisher was removed within days of the detection of the second issue. I apologize if my opening statement did not clarify all the facts, but I did try to address them in my opening statement and would be happy to provide more information.

Mr. DINGELL. I think more information on this matter would be useful, Doctor, and we'd appreciate that, for the record. The gentleman from Colorado continues to be recognized.

Mr. SCHAEFER. I thank the Chair. Dr. Bivens, I noticed that Dr. Poisson was prohibited from serving on the Public Health Advisory Committee and was barred from receiving Federal funds or grants for a period of 8 years. Is this a maximum debarment?

Mr. BIVENS. It's very close to the maximum debarment that the Department imposes.

Mr. SCHAEFER. What is the maximum?

Mr. BIVENS. The longest one I know of is 10 years. There may be longer ones, but the only one I'm familiar with, which is longer than 8 years, is another scientific misconduct case. The modal term for debarments across the Department is on the order of 3 years. So anything in excess of 3 years we have to make an especially strong case for to the debarring official.

Mr. SCHAEFER. Is that regulation?

Mr. Bivens. I don't know that the term of debarment is written into the regulation, no, sir. But it's a practice that the Assistant Secretary for Management and Budget applies, in which 3 years is the usual. If there are more serious offenses, it can be longer. I can't say much more than that because I don't want to speak for the Assistant Secretary for Management and Budget.

Mr. SCHAEFER. I guess the question I have is that if somebody is guilty of fraud, why should they ever, ever be eligible to receive Federal grants?

Mr. BIVENS. That's a perfectly legitimate question. I think in some cases, they should never be eligible to receive grants. I guess I would be surprised of Dr. Poisson ever came in for an NIH application in the foreseeable future. But, nevertheless, I'm stuck with the practice of the Department and the standard terms of debarment. We have to argue quite strongly for debarments in excess of 3 years.

It is certainly arguable that 8 years is insufficient.

Mr. SCHAEFER. I would certainly agree with that. I will yield to my friend here for a minute. Let me regroup and see what else I've got here.

Mr. DINGELL. I want to come back to the question. You had two studies here and we dealt with the question of notification. We have talked of the prevention study, but we have not talked to the treatment study.

On the treatment study, has there been any notification either of NIH or of the participants in the study with regard to the possibility of increased risk of uterine cancer?

Mr. BRODER. With the Chair's permission, I'd like Dr. Chabner to address that.

Mr. DINGELL. Can you help us out with that, please, Doctor?

Mr. CHABNER. May I address that, sir?

Mr. DINGELL. Certainly.

Mr. CHABNER. Yes. On January 12, we issued new information to all of the treatment centers to inform them that informed consents must be changed to reflect new appreciations of what the risks of endometrial cancer were and the fact that we had just learned that deaths had been reported.

Mr. DINGELL. Was that done, do you know?

Mr. CHABNER. I do, sir, because——

Mr. DINGELL. Was it done by the centers?

Mr. CHABNER. Yes, sir. I've gotten information back from our cooperative groups who participate in these—who sponsor and direct these studies that the amendments have been changed; that is, the informed consent documents have been changed for all the studies and that patients are being informed at this moment.

If I may point out, sir, some of the studies already had within them the risk of death and they had within them descriptions of endometrial cancer risks. So what we're doing is making sure all the studies come up to a certain standard.

These studies are slightly different than the prevention trials, sir, in that this is the commercially-available use of this agent; that is, tamoxifen is commercially-available and many thousands of women take it. So we are trying to have our informed consent documents measure up to the latest information that we get from the drug company, as well.

Mr. DINGELL. I applaud this. We've come back to the prevention study that we have not been discussing at this minute. We still confront the problem that we don't know what has happened with regard to the women who are participants in that study in terms of upgrading the notice that they had of potential risks. Is that right?

Mr. CHABNER. Sir, my understanding is that at all the sites, information is provided for both the prevention trial and the treatment trial. Just as others have said, I cannot assure you today that every last woman has been informed.

Mr. DINGELL. I accept that and I don't want you to feel I'm interrupting you. I'm satisfied with your answer. But we then confront the little additional difficulty that we don't know yet what the requirements are with regard to warnings to participants in the studies.

Am I fair in that appreciation, Dr. Varmus or Dr. Broder?

Mr. VARMUS. We do require that they be informed. But you are asking whether we know that everybody has been informed and we do not know that.

Mr. DINGELL. But what's in the protocols with regard to informing participants in these studies about changes in circumstances; in other words, additional risks that might become known as the process goes forward? Do you have some kind of a generic policy with regard to that or do you not?

Mr. BRODER. While they're looking for the documents, I will speak for the NCI. There is a requirement that institutions, as part of their human subjects assurance, a broader policy than the NCI, must have a process for informing patients about research risks and benefits, that they must have an institutional review board that must approve such changes, and that they will update and bring new information both to the institutional review board and to the patients as new facts become available.

Mr. DINGELL. So we would have a problem, then, if that kind of notice had not been given to the women who were participating in the studies.

Mr. BRODER. We have a problem whenever information flow is blocked.

Mr. DINGELL. Could you check and find out for us, please, gentlemen, whether or not the information on these matters has flowed through in compliance with the regulations at NCI?

Mr. BRODER. I will give you a status report within 24 hours.

Mr. DINGELL. It doesn't have to be 24 hours. Just at your earliest comfortable convenience. We're speaking here as friends, we want you to understand.

Mr. BRODER. We appreciate that.

Mr. DINGELL. This to Dr. Varmus. Doctor, how seriously do you view the withholding of information about tamoxifen-related deaths by one of NCI's largest grantees and one of the largest grantees from the FDA and potential withholding of information from NCI, potential withholding of information from FDA, and from the American public? Is this a serious matter or not?

Mr. VARMUS. Of course, it's a serious matter, extremely serious.

Mr. DINGELL. Are you concerned?

Mr. VARMUS. Of course, I'm concerned.

Mr. DINGELL. Figure we maybe ought to take a look at the rules and regulations and see whether they're inadequate?

Mr. VARMUS. The regulations with respect to the reporting of information to us, I think, is unequivocal. What we're trying to establish here, because you've raised an interesting question, is the regulations as they pertain to our assurance that any individuals engaged in any clinical research studies be informed through the consent form of any changes in our information.

There is, it appears, still a degree of local autonomy with respect to how the consent forms are constituted. We are obligated to inform the institutional review boards of any new information that is pertinent to the writing of the consent form. It is then in the jurisdiction of that institutional review board to review the information and to make a decision about how they're going to change the form.

The form must then be returned to us so that we can review it and advise them. But you've raised a question that is new to me, frankly, with respect to the degree to which we can impose our will upon the rewriting of a consent form in response to new information. There is, at the moment, some autonomy accorded to the local institutional review boards.

Mr. DINGELL. Let's get down to a document that has just fallen into the hands of the committee. Yesterday afternoon, Zeneca Pharmaceuticals produced a number of documents to the subcommittee regrading their knowledge of cancers and deaths associated with the B-14 trial. One such document is an internal Zeneca memorandum, dated July 7, 1993. I'm going to quote from parts of it here.

It says as follows, and I'm quoting, "I then proceeded to tell Dr. Fisher that the increasing number of patients within the B-14 trial developing endometrial cancer while on Nolvadex did prompt us to look at this issue more closely. Upon careful review of the data, we felt that there was an increased risk to develop endometrial cancer with Nolvadex and that we will modify our label to reflect this. I also commented that it was impossible to precisely quantitate the relative risk, although, qualitatively, it did appear that there was a slight increase incidence."

"Dr. Fisher agreed with this assessment and felt that we were acting responsible", and that's a direct quote, "by changing our label. I commented to him that at least in the United States we would have to make minor changes in our label, but I did not see these changes having a great impact on the treatment of patients with confirmed breast cancer, and also on the U.S. prevention trial, since the protocol did include the B-14 data, as well as the Swedish data, and that this potential risk was noted on the consent form."

"However, I did comment that it did have more of an impact on the European trial, which would require that the protocol and the consent form be modified. Dr. Fisher was told that Dr. Cusick had been notified and the European protocol and consent will be modified. Dr. Fisher appreciated our willingness to provide him with a copy of the justification document for this label change. Dr. Fisher did comment about the potential negative publicity that could occur. In particular, this could be the bullet being sought by the health industry in the U.K. to stop the European prevention trial. If this is the case, that would have a major effect in the United States. He agreed that we should be prepared for this potential negative outcome."

Now, Dr. Broder, are you aware of this exchange between Zeneca Pharmaceuticals and Dr. Fisher or the fact that the people in these studies were concerned about how the B-14 trial would effect the prevention trial?

Mr. BRODER. I was not aware.

Mr. DINGELL. Beg your pardon?

Mr. BRODER. I am not aware.

Mr. DINGELL. What do you make of this memo? It's something that should have been brought to your attention or to the attention of the NCI, should it not?

Mr. BRODER. I agree. I would need to consult with Dr. Ford. May I just take this document to Dr. Ford?

Mr. DINGELL. Sure. Without objection, these documents relative to Zeneca Pharmaceuticals will be inserted in the record at the appropriate place. [See p. 214.]

Go ahead, Doctor.

Mr. BRODER. I'm quite disturbed by some of the things that you just read.

Mr. DINGELL. I think it would be unfair for me to try to compel you to comment, but it is a document which I think should concern us. Is it not? It tends to indicate that perhaps maybe the pharmaceutical house and Dr. Fisher have not been sufficiently forthcoming, though, does it not?

Mr. BRODER. I'm comparatively concerned that I don't disagree with what you have just said.

Mr. DINGELL. Now, let's look at this situation. Here we've got the University of Pittsburgh. Now, the University of Pittsburgh solicited a million dollars from Zeneca for the endowment of a chair. They wound up getting $600,000. This is while the test of this particular pharmaceutical is going on.

Does that seem to be quite cricket? Dr. Varmus, do you want to comment?

Mr. VARMUS. I personally have concern about engaging in that kind of relationship.

Mr. DINGELL. I wonder. Does it pass the Aunt Minnie Sniff Test?

Mr. VARMUS. What test? I'm sorry.

Mr. DINGELL. If Aunt Minnie were to sniff this, what would she say?

Mr. VARMUS. Can you explain the test to me, sir?

Mr. DINGELL. Well, Aunt Minnie is somebody we use around here because she has a sensitive nose. What we're trying to figure out is would she like the smell of this or not.

Mr. VARMUS. Probably not.

Mr. DINGELL. Here we've got the University of Pittsburgh. Let's go through some of the times that we've cut their track, just see. We had Dr. Steven Bruening. He pled guilty to false statements in connection with the making of a number of tests with regard to youngsters, hyperactive youngsters and mentally-impaired youngsters, and he said that medication should not be given them to suppress the activity. He did this on the basis of studies which he said he had made, which, in fact, he did not make.

Then we had a fellow by the name of Dr. Herbert Needleman. He studied the exposure of children to lead. Now, this was reviewed by the reviewing authorities and they said that the reports were false, but they said that there was no misconduct.

Then we had a fellow by the name of Dr. Charles Bluestone. He took large sums of money from a company that was selling drugs that he was studying. I wonder if we ought not get the University of Pittsburgh in here to talk to us about these matters.

Mr. VARMUS. I have inquired myself of the University of Pittsburgh about these matters, sir.

Mr. BRODER. We have received correspondence from them on these points.

Mr. DINGELL. What do you have to comment either with regard to the correspondence or——

Mr. VARMUS. I first learned from a letter addressed to the Secretary from Senator Rockefeller and Mr. Waxman, I believe, that there was a report in Who's Who that included Dr. Fisher's entry claiming that he occupied the ICI professorship.

I asked Dr. Chabner, who was then in Pittsburgh, to obtain for me some information about this relationship, which seemed to me not to pass my own sniff test. What we learned was that the chair had been partly endowed by the ICI and that Dr. Fisher had not occupied that chair. Now, we looked ourselves in American Men and Women of Science and found an entry that included that professorship under his name.

I further inquired of the university about what seemed to be discrepancies in these accounts and I was told that was a clerical error and that a secretary had, to Dr. Fisher's regret, included this in his biographical listing, that it was not accurate.

I, myself, think that it is difficult to maintain the appearance of propriety and possibly the practice of propriety if one's own department is receiving a large endowment for a professorship from a company that's supplying a drug that's being used in a clinical study being carried out by that investigator.

Universities are under financial stress, but the issue of the credibility of research that results from university activities is a greater issue, in my own mind.

Mr. DINGELL. I gather Dr. Fisher is still being compensated by the university.

Mr. VARMUS. Yes, he is.

Mr. DINGELL. So whether he occupies the chair is really of limited importance. The question here is the money, not who occupies the chair. Somebody else is occupying the chair, but chairs seem to be somewhat fungible. In other words, one fellow can sit in them

or another fellow can sit in them. It doesn't really make too much difference as long as somebody plays the chair.

Mr. VARMUS. I'm just providing you with the answers I received.

Mr. DINGELL. Did you say nobody occupies the chair?

Mr. VARMUS. Apparently, the amount of money is insufficient to generate the income that would be required to pay a full salary. Now, at some institutions, I know that a chair may not pay the full salary, but still constitute a chair. It's a matter of definition.

Mr. DINGELL. I have seen nothing that would indicate on my part any concern about the university being distressed about this situation. They still got the money, right?

Mr. VARMUS. Yes.

Mr. DINGELL. We have, then, a question about the status of the University of Pittsburgh's assurances. What is the status of the University of Pittsburgh's assurances that the—at your operation, if you please?

Mr. CHABNER. I'm sorry, sir. I don't understand the question.

Mr. DINGELL. The question was for Dr. Bivens. But, again, we are blessed with our inadequate——

Mr. BIVENS. An important part of ORI's work is to review the policies and procedures that are used by institutions, what policies and procedures are in place to satisfy the regulatory requirement for an assurance, and to see if the institution is following its own policies and procedures.

We do have a major compliance review underway right now, reviewing University of Pittsburgh and its compliance with the PHS regulations. We are first looking at their existing policies and procedures to see if they comport with the requirements of the regulation and then we are looking at the historical record of how they have handled inquiries and investigations to see if they fit with their own policies and procedures.

If we identify any problems, we will require immediate corrective action.

Mr. DINGELL. The assurance that we're referring to is, of course, the assurance of scientific integrity, isn't that right?

Mr. BIVENS. That's correct, sir.

Mr. DINGELL. What happened between ORI and the University of Pittsburgh regarding this assurance?

Mr. BIVENS. I don't recall in my tenure any specific interchange between ORI and Pittsburgh related to their assurance.

Mr. DINGELL. Should you consider suspending this and didn't, in fact, you consider suspending the scientific integrity assurance pending improved performance by the university?

Mr. BIVENS. Not while I was Director. I became Director in January 1993. There may have been a prior history with the old offices, OSI and OSIR, and even my old office, OSIR, I don't recall that kind of interchange. But we certainly have that option of suspending the assurance.

Mr. DINGELL. Clearly, your predecessor had that option because these events occurred apparently just previous to the time that you assumed your current responsibilities.

Can you tell us what the records of your agency show?

Mr. BIVENS. I would have to look at those. I'm not familiar with them right now.

Mr. DINGELL. Would you do that and make that information available to the committee, please?

Mr. BIVENS. I'd be glad to.

Mr. DINGELL. The Chair is going to recognize the gentlewoman from Pennsylvania.

Ms. MARGOLIES-MEZVINSKY. Thank you, Mr. Chairman. Dr. Broder, for the sake of fairness, it's important to emphasize, I think, that Dr. Fisher has not only not been found guilty of scientific misconduct, he's not even under investigation. Is that correct?

Mr. BRODER. That is absolutely correct.

Ms. MARGOLIES-MEZVINSKY. You have removed him as a principal investigator, as administrator of the NSABP program. We have been told that he was removed because NCI had some doubt about his continued fitness to serve as principal investigator. We've gotten some calls in our office from some of his patients who say that he was a really fine physician, saved their lives, all those things.

Can you describe for the subcommittee the principal of fitness and how you applied it in his case?

Mr. BRODER. Thank you for the question. The word "fitness", if that's the right calculus that we would use here, does not go to——

Ms. MARGOLIES-MEZVINSKY. What word would you use?

Mr. BRODER. I would use suitability. But I didn't do a legal analysis and I don't think we did the kind of exact word. But, basically, the bottom line is that what we felt was that Dr. Fisher could not be the individual with whom we corresponded on matters of the performance of this grant, which had to do with things such as specific compliance with our rules, specific implementation of auditing procedures, proper notification of problems, all the things that we have talked about and many of the issues that I raised in my opening statement.

This was not a determination and should not be construed as a determination that Dr. Fisher is not fit to function as a surgeon or as a clinical scientist. That is not what we are saying and that is not what we are talking about today. That is why I tried in my opening statement to draw a distinction between his formidable intellect and formidable record in spite of all the things that we talked about, his contributions. Dr. Fisher is a Lasker Award winner. He has made a number of contributions.

My position is none of that matters in our analysis of who shall run a grant that we administer. It has to do with the performance of the individual here and now.

Ms. MARGOLIES-MEZVINSKY. Dr. Varmus?

Mr. VARMUS. Yes. I agree with that statement.

Ms. MARGOLIES-MEZVINSKY. And you support the NCI's action regarding Dr. Fisher.

Mr. VARMUS. The NCI recommended to the university that Dr. Fisher be replaced as the director of that project for administrative cause, and I agree with that assessment.

Ms. MARGOLIES-MEZVINSKY. How do you view this standard of, whatever you want to call it, fitness, suitability, and how do you believe it should be applied in other cases?

Mr. BRODER. To whom is the question?

Ms. MARGOLIES-MEZVINSKY. Dr. Varmus.

Mr. VARMUS. This is a case-by-case analysis. It's an unusual circumstance, but we had a very significant problem on our hands, which is the focus of this hearing today; namely, that the precipitating feature here was the failure of the NSABP to publicly distribute the results of the ORI investigation and the reanalysis of the NSABP study, known as B-06. Under those circumstances, it was proper that the NCI evaluate administrative practices at the NSABP and what they found were a number of failures of administrative oversight that, to my mind, called for Dr. Fisher's replacement.

Now, in similar circumstances, I would advise the same thing. This is an unusual occasion in the history of clinical research in this country. At the moment, I don't see any clear simple prescription for the conditions under which similar actions would be advised.

Ms. MARGOLIES-MEZVINSKY. We are talking about the application of a principal, correct?

Mr. VARMUS. Yes.

Ms. MARGOLIES-MEZVINSKY. Are we applying the application of this principal consistently?

Mr. VARMUS. We are, but we don't have very many cases to apply it to at this point.

Ms. MARGOLIES-MEZVINSKY. Dr. Broder, does the principal of fitness or suitability also apply to intramural NCI scientists?

Mr. BRODER. It most certainly does.

Ms. MARGOLIES-MEZVINSKY. What about Dr. Gallo?

Mr. BRODER. Is there a specific question about Dr. Gallo or do you wish me just to make a general comment?

Ms. MARGOLIES-MEZVINSKY. Is it still under consideration or are you applying that principal?

Mr. BRODER. Dr. Varmus and I have discussed a number of issues related to Dr. Gallo. The issues involving Dr. Gallo have until recently been complicated by a formal inquiry process that has gone from OSI to ORI. We were awaiting the results of that process to end and also to have the kind of factfinding that we needed to do in order to make a decision.

In Dr. Fisher's case, we believed that there was sufficient and compelling facts at our disposal, specific facts that related to his specific performance in a specific way, including, among all the other things, our detection of a report of yet an additional site in Canada which subsequently turned out to be an indicia of serious data manipulation in another patient, which Dr. Fisher had still, after all of our warnings, still not reported to us.

So we believed that the facts in that case could allow but only one conclusion in this specific situation. But we will review the situation and the facts of Dr. Gallo's case. Staff members have been very kind in providing information to me and I believe will be meeting with me again.

Ms. MARGOLIES-MEZVINSKY. I don't think we're trying to get into the personnel action. I think we're trying to get into the principal, if you're going to apply the same principal.

Mr. BRODER. The answer is yes. We will apply it to all grantees and to the intramural program. But the jobs may be different.

There may be different aspects of what you apply to each different employee. Dr. Fisher has the right to assert to us that he's a very good surgeon and a very good clinical researcher and were we dealing with a grant that uniquely was funding him as a surgeon or as a clinical researcher or as someone who took care of patients, as you may have implied, we would not be saying we have concerns about his capacity to provide excellent state-of-the-art care to a patient. That is not the basis of his removal from being a principal investigator.

Ms. MARGOLIES-MEZVINSKY. Do you believe that the principal of fitness, suitability or whatever you want to call it should apply to all NIH intramural scientists?

Mr. VARMUS. Yes, I do.

Ms. MARGOLIES-MEZVINSKY. Dr. Broder, isn't it true that NCI has always possessed the authority and the ability to apply these standards and to take the actions that you have taken in this case?

Mr. BRODER. Yes.

Ms. MARGOLIES-MEZVINSKY. Have these standards and actions previously been routinely applied or are we seeing something new?

Dr. BRODER. I am not aware of—I personally am not aware, and staff will have to inform me. I am not aware of the NCI asserting its rights under the Code of Federal Regulation and other applicable statutes to demand data from an investigator, disseminate that date, publish the data without the investigator's necessary involvement even, possibly even against the will of the investigator. I am not aware of that principal ever having been implemented. But it has been now and we will not hesitate to do it again if a fraud issue comes up.

It has a downside, however, in that it could create situations in which we at NCI are making statements which are at variance from a formidable intellect and leader in a field, and that also has its downsides. That's why our hope had been—this is an explanation, not an excuse.

Our hope had been that we could reach a situation where Dr. Fisher, with our assistance, would take the lead to first come forward with all the different issues.

Ms. MARGOLIES-MEZVINSKY. Dr. Varmus, do you support NCI's willingness to exercise this existing authority and will we see similar actions, if necessary, across the board at NIH?

Mr. VARMUS. I support it in this case and, by implication, I would support it in other situations that are comparable.

Ms. MARGOLIES-MEZVINSKY. Thank you. I yield the balance of my time, Mr. Chairman.

Mr. DINGELL. The Chair recognizes the gentleman from Ohio.

Mr. BROWN. Thank you, Mr. Chairman. Dr. Broder, on the subject of willingness to deal forthrightly with scientific fraud in, I believe, July of 1991, you were briefed by OSI concerning its findings of falsification and its findings of fabrication of St. Luc data.

Describe, if you would, what you were told, what directives you issued pursuant to that briefing.

Mr. BRODER. Yes. I believe the committee has a memo for the record prepared by Dr. McFarland in this regard. I received a summary from individuals with firsthand knowledge of the fraud at Le Hopital St. Luc in Montreal. It was very clear to me that there was

a serious problem of overt fraud and that the issue had to be dealt with forthrightly and effectively.

We determined that we would cooperate with ORI and provide whatever resources we could. I determined at that time that the only course of action that could be taken would be to segregate the data from the Le Hopital St. Luc and permanently pull it out of future analyses, but providing the data—providing analyses both with and without the data, but permanently notifying individuals that the data had to be pulled out, and, also, taking steps to appropriately reanalyze and republish the data with the appropriate interactions with the Office of ORI, although it may not have been called ORI in that era.

It was at that point the predecessor organization for ORI.

Mr. BROWN. So I take it NCI and Pittsburgh simply didn't follow your direction.

Mr. BRODER. Speaking as to the effects of the University of Pittsburgh, they certainly did not follow our very constructive criticisms. As to NCI staff, I will accept responsibility for this issue.

Mr. BROWN. This seems to be the picture. We have the Director of NCI telling subordinates to have University of Pittsburgh reanalyze the data, republish the analysis, not publish further studies using this falsified fabricated data; yet, every single directive was disobeyed, ignored, taken too lightly, whatever. Why? What happened?

Mr. BRODER. I believe it is, in part, a function of Dr. Fisher's formidable reputation and I believe that the staff were attempting to negotiate a collegial non-confrontation way of dealing with a pioneering figure who obviously knew a great deal. I believe there was an excessive level of collegiality and a higher level of tolerance than is now the case. That is probably the best way that I can summarize this.

Staff simply did not wish to confront and order Dr. Fisher, who, after all, is the person that had made many contributions, had a great deal of status in the scientific community. I believe that is, in part, responsible for what happened.

The other issue, which is of no comfort to the committee or the public, but which is, I think, one of the factors that should be put on the table, is that the staff felt that Dr. Fisher had been right on a number of occasions that, in fact, there were no changes that would come from this and that other studies already available were confirming the value of breast-sparing surgery. So all of those factors came into the mix.

I do believe that had there been a public health hazard, that the other steps would have been taken, but that's of no consolation to the committee and I accept your point.

Mr. BROWN. Dr. Varmus, according to Dr. Broder, it sounds a little bit like Congress, collegiality, protecting people, people protecting themselves, all of that. It sounds like the criticisms that people, sometimes rightly, level at this institution.

What is the rationale beyond that for why Dr. Fisher and his colleagues would continue to submit and publish papers that are known to contain that false data? What, building on what Dr. Broder said, is that rationale for Dr. Fisher to do that?

Mr. VARMUS. I think these are questions that should be addressed to Dr. Fisher. But I think there are some potential explanations that have to do with the desire to publish the findings of studies that have been carried out in multiple-institutions.

I cannot myself condone the inclusion of data from the St. Luc Hospital once fraud at St. Luc's had been ascertained. To my way of thinking, information from that hospital should have been excluded from any further publication. So I don't want to pretend to understand how that came to be. I think you really need to address those questions to Dr. Fisher and other members of the NSABP.

Mr. BROWN. Let me ask it a different way. Let me ask Dr. Broder in this case. The subcommittee staff has found that as early as July of 1992 that NCI officials were admonishing Dr. Fisher, admonishing his colleagues to upgrade and strengthen auditing procedures. What was the response of Dr. Fisher and what was the response of his colleagues to those repeated requests from NCI?

Mr. BRODER. I would say that Dr. Fisher's response to us was quite disrespectful of the role that government employees play and quite disrespectful of the status and functions that we have and, I think I'm accurately paraphrasing, basically said words to the effect of who are you to criticize me, I know how to do clinical trials, I've been doing them before you were a doctor.

That's not literally what he said, but I am giving you my editorial response. I believe our staff referred to some of his things and tried to give him constructive criticism, which he rejected out of hand.

Mr. BROWN. So what's the next step? What was the next step? If he responded to you that arrogantly and with that haughtiness, if you will, and with that self-certitude or self-righteousness, what was your response back?

Mr. BRODER. I believe the staff continued the process of negotiating with him and bending him to the things that needed to be done. They did, in fact, negotiate successfully for him to accept certain changes, at least as we were informed about them. We made our point with respect to the institution of data safety monitoring boards and other things that he was instructed to do.

They had been given assurances that papers were being prepared and that reanalyses were coming, and I think that that—it was a slow process, but I believe, speaking for the staff, they thought they were moving in the right direction and that they were preserving Dr. Fisher as a force who could contribute and continue to do good in a method that was collegial.

Mr. BROWN. We have seen a number of reports of NSABP audits that reflect significant discrepancies in the audited records of various research sites. What are NSABP's duties and responsibilities regarding audit follow-ups and recommendations?

Mr. FRIEDMAN. Currently, under the new branch which has been just identified and even prior to the establishment of that branch, the NSABP is having a complete overhaul of how their on-site auditing is conducted. If you're interested, I can describe the inadequacies of the previous program or I can simply give you information about the current program.

Mr. BROWN. Do both, please.

Mr. FRIEDMAN. All right, sir. In the past, rather than having an audit where investigators would go to the site that the research is being conducted and to examine records from that site and look for supporting information, the way the NSABP conducted their audits was to have individuals go xerox records and bring them back to Pittsburgh. In addition, whereas our other cooperative groups—and this is a very important point, sir.

In contrast to how our other cooperative groups operate, the number of charts sampled at each of these research sites was relatively small. Instead of having a larger number of charts sampled from a larger enrolling institution, they had a small fixed number of charts examined at each institution.

This was not—although it was defended by the NSABP, this was not a system that we felt was entirely appropriate or would be as efficient as we would like. We were very concerned about the discovery of the fraud at St. Luc Hospital and wanted very much to try and look carefully at their system and bring it at least up to the standards of other cooperative groups.

Currently, the monitoring program for the NSABP is to have a larger number of charts sampled, to have researchers go to those individual sites and actually look at the primary data, an x-ray or an EKG form or whatever is at that site, to confirm the reliability and truthfulness of that.

We have been very concerned about the whole credibility of the lumpectomy trial because, as was expressed this morning, there is so much public concern about it and it would be wrong for us to not be attentive to that concern. We have been very careful to go and look at more than 850 research records, the primary patient charts of patients who enrolled in the B-06—that is the lumpectomy trial—to examine those records to see if there's any systematic fraud or falsification.

We also examined a number of other charts, all together almost 1,400 charts, looking at many different studies, to try and confirm that, in fact, despite the unsatisfactory nature of the system that existed previously, that we could still have confidence in the conclusions that these investigators were describing.

Mr. BROWN. Thank you, Mr. Chairman.

Mr. DINGELL. The Chair thanks the gentleman. The gentleman from Colorado.

Mr. SCHAEFER. Thank you, Mr. Chairman. Just a few wind-up questions. Dr. Varmus, I understand that approximately a million dollars of the taxpayers' money was used in the St. Luc research. Are there any efforts underway to determine whether this money can be reclaimed?

Mr. VARMUS. Yes, there are. We've been trying to reclaim the money. As you understand, there are jurisdictional problems, with the St. Luc Hospital being located in Montreal, and we've asked the Department of Justice for help in trying to recover the funds.

Mr. SCHAEFER. Does the University of Pittsburgh—after you.

Mr. DINGELL. Would you give us a report on the status of matters with regard to the assistance of the Department of Justice, please?

Mr. VARMUS. For the record, yes.

Mr. DINGELL. Not right at this minute, but just when it's comfortable.

Mr. VARMUS. Absolutely.

Mr. SCHAEFER. May the University of Pittsburgh have any liability in this?

Mr. VARMUS. They might. We're looking into that as well.

Mr. SCHAEFER. That's all part of it. And this is what we're going to get an update on.

Mr. VARMUS. We can provide you with a detailed account of that from our general counsel.

Mr. SCHAEFER. Can you tell me if these efforts to retrieve the money were begun before or after the subcommittee started looking at this?

Mr. VARMUS. As far as I know, after.

Mr. SCHAEFER. After.

Mr. VARMUS. After I was informed of some of these concerns.

Mr. SCHAEFER. Right.

Mr. VARMUS. As you know, I'm new at NIH, but when I heard about them, we began to look into this question.

Mr. SCHAEFER. So once our subcommittee began looking into this matter, then steps were taken to try to reclaim it.

Mr. VARMUS. That's correct.

Mr. SCHAEFER. I thank the subcommittee for that. It's a million dollars. Are you looking in your files to see if there's attempts being made to recover taxpayers' dollars in other instances where fraud was involved?

Mr. BRODER. Sir, we are. We consider that we—we have a manual that has been implemented in which fraud will always be presumed, a rebuttable presumption, but will always be presumed to indicate recovery. Then we will act against the grantee according to the advice that we receive from the Office of General Counsel and according to applicable principals of law and Federal regulations.

This will be automatic and it is clearly understood in our grants management process and so on.

Mr. SCHAEFER. Had this been done before this situation, before our subcommittee started——

Mr. VARMUS. I've been informed by Dr. Baldwin it's been done twice before.

Mr. SCHAEFER. OK. Mr. Chairman, I'm finished.

Mr. DINGELL. The Chair thanks the gentleman. Dr. Bivens, what other cases presently active at ORI or other during your tenure that have been closed with a finding of misconduct involved clinical trials or impact upon the public health?

Mr. BIVENS. I believe that the St. Luc case is the only one in which there was a confirmed scientific misconduct finding related to a clinical trial.

Mr. DINGELL. Which one would that be? Can you tell us about presently active ones?

Mr. BIVENS. Presently active ones?

Mr. DINGELL. Yes, sir.

Mr. BIVENS. My understanding is that there is an investigation underway and an inquiry underway on two trials funded by the National Eye Institute.

Mr. DINGELL. National Art Institute?

Mr. BIVENS. Eye Institute. I'll be glad to provide more information on those. I don't have it ready at hand at the moment.

Mr. DINGELL. If you please.

[The following information was received:]

REPORT ON ACTIVE ORI CASES INVOLVING MULTICENTER CLINICAL TRIALS

A. Investigation into possible falsification and fabrication of data in the PHS funded COLLABORATIVE OCULAR MELANOMA STUDY at Northwestern University Medical Center (93-27) and The Cleveland Clinic Foundation (93-28)

Funded by the National Eye Institute (NEI), National Institutes of Health, The Collaborative Ocular Melanoma Study (COMS) consists of two multicenter, randomized controlled clinical trials designed to investigate the efficacy of radiation therapy compared to surgery in prolonging the vision and survival of patients presenting with choroidal melanoma, a rare intraocular cancer.

Approximately 1500 new cases of choroidal melanoma are diagnosed each year within the U.S. The liver is the most frequent site of metastasis. The median survival after diagnosis of metastatic disease is 6-9 months; therefore, choroidal melanoma is indeed life threatening. The most widely used treatment for choroidal melanoma of all sizes has been removal of the eye (e.g., enucleation). Radiation therapy has been advocated as an alternative treatment with the goal of preserving the eye and possibly some vision in the affected eye.

Patients presenting with unilateral choroidal melanoma classified as "medium" in size are randomized with equal probability to either enucleation or radiation therapy by application of a radioactive plaque sutured to the eye over the base of the tumor. Patients with large tumors are randomized with equal probability to either enucleation or a five day course of external beam radiation therapy followed by enucleation. (Controlled Clinical Trials, 14:362-391, 1993).

Clinical data on COMS-eligible patients in each of the more than 40 participating centers is forwarded to the COMS Coordinating Center for entry into the study database and statistical analyses. The Coordinating Center is located at the Wilmer Ophthalmological Institute, The Johns Hopkins University, Baltimore, MD, and is supported by a cooperative agreement.

No results of the COMS clinical trials have been published at this time. The protocol for the study was published in 1993 and is referenced above.

The COMS Coordinating Center identified possible falsification and fabrication of records submitted from two of the participating COMS centers, the Northwestern University Medical Center and The Cleveland Clinic Foundation, on April 14, 1993, and on June 28, 1993, respectively. The NEI program officer was alerted about the discrepancies in the Northwestern COMS data on

May 21, 1993. Similar discrepancies in data from the Cleveland Clinic Foundation program were revealed at a meeting of the COMS Data Safety and Monitoring Committee on October 4, 1993.

ORI was informed of the data reporting discrepancies at the Northwestern COMS center on August 26, 1993, by a telephone call from the NEI misconduct policy officer. ORI was informed of the data reporting discrepancies associated with The Cleveland Clinic Foundation COMS center on October 5, 1993, during a meeting between NEI and ORI staff which had been scheduled to discuss the Northwestern findings.

The Northwestern University Medical Center:

The Northwestern University Medical Center has been a participant in the COMS program since 1986. Until recently, the Northwestern COMS program registered the largest patient enrollment (103) of all the participating COMS centers nationwide and in Canada. In 1992-1993, Northwestern University received $127,700 in PHS support for its participation in COMS.

Identified discrepancies in the reporting of clinical trial data at the Northwestern COMS Center were brought to the attention of University officials and to the COMS Coordinating Center on April 14, 1993, by the Principal Investigator. He stated that inaccurate data (e.g., misrepresentation of examination dates and other dates associated with laboratory tests, X-rays, etc.) were supplied to the COMS Coordinating Center by the Northwestern COMS clinical coordinator who was immediately placed on leave from the program; employment was terminated later in April without an official University inquiry. The COMS Coordinating Center dispatched an audit team to the Northwestern COMS center on April 22 and again on June 1, 1993. A University committee of inquiry was established on May 20, 1993, to examine the issue of possible scientific misconduct within the COMS program and to make a recommendation to University officials regarding the need for a full investigation. The inquiry committee submitted its recommendation that an investigation was warranted in a report to the Vice President for Research and Graduate Studies on October 5, 1993.

The Division of Research Investigations (DRI) in ORI was notified on August 26, 1993, by the NEI of data reporting discrepancies at the Northwestern COMS center and told that the institution was conducting an inquiry. DRI met with the NEI misconduct officer to obtain additional information and a copy of the COMS Coordinating Center audit report, and informed Northwestern University officials on October 12, 1993, of its intent to open a case and to conduct a direct investigation. The DRI requested the University to cease its investigation of the COMS matter and to secure all COMS patient medical and research files. Based on the Coordinating Center audit report and the Northwestern inquiry report, DRI identified the potential respondents in the case.

DRI visited Northwestern University on February 7-11, 1994. Medical and research files of all 103 eligible patients enrolled in the COMS program were reviewed against data submitted to the coordinating center. COMS Coordinating Center staff provided technical support during the review. Several key witnesses and all but one of the possible respondents were questioned and their testimony recorded. The DRI analyses of the evidence obtained at the site visit and final conclusions remain to be finalized at this time.

There were a number of data items reported for the Northwestern patients which could not be confirmed because documentation was not available. These issues remain to be resolved.

The Cleveland Clinic Foundation:

The Cleveland Clinic Foundation has been a participant in the COMS program since 1986; investigators have entered 24 patients on the study. The Cleveland Clinic Foundation receives funds through a subcontractual agreement with the COMS Coordinating Center at the Johns Hopkins University; funds allocated to The Cleveland Clinic Foundation COMS program for the ninth year (1993-1994) of the study total $20,762.

Identified discrepancies in the reporting of clinical trial data from The Cleveland Clinic Foundation came to the attention of the COMS Coordinating Center through a routine audit of patient files by a representative of the Coordinating Center on June 28, 1993. The initial purpose of the visit by the Coordinating Center representative was to review the current status of clinic operations and to assist in resolving any problems that arose since the previous clinic visit or that were identified during the current visit. Identified discrepancies included:

1) blood test results were reported as normal but no record was available to confirm the test was performed;

2) falsification of dates for patient examinations so as to be compatible with protocol restrictions;

3) reporting of blood test results as normal when the results were abnormal;

4) a COMS certified examiner was identified as having performed an evaluation when the evaluation was actually performed by a non-COMS certified staff member.

Although the data reporting discrepancies associated with The Cleveland Clinic Foundation COMS center were known to the COMS Coordinating Center at the end of June 1993, this information was not brought to the attention of the NEI until the October 4, 1993, meeting of the COMS Data Safety and Monitoring Committee.

The NEI Program Officer alerted the NEI misconduct policy officer, on October 4, who, in turn, alerted the ORI on October 5, 1993.

On October 12, 1993, DRI informed institutional officials at The Cleveland Clinic Foundation of its intent to open a case (DRI 93-28) and to conduct a direct investigation into the alleged scientific misconduct involving The Cleveland Clinic Foundation COMS program. The institution was instructed not to initiate its own inquiry or investigation and to secure all research and medical records of every patient affiliated with the COMS program. Based on the Coordinating Center report and their positions with regard to the COMS project, DRI named the possible respondents in the matter.

The DRI site visit to The Cleveland Clinic Foundation COMS center was conducted on December 6-9, 1993. Medical and research files of the 24 eligible patients enrolled in The Cleveland Clinic Foundation COMS program and of 37 patients screened but not eligible for the COMS program were evaluated for possible fabrication and/or falsification of reported data. COMS Coordinating Center staff provided technical support during this review. Key witnesses and all respondents were interviewed and their testimony recorded.

The DRI has concluded its fact-finding of The Cleveland Clinic Foundation COMS program and is preparing its final report.

ORI has briefed the Office of the Inspector General, HHS on DRI #93-27 and #93-28. Additionally, ORI met with officials from NEI on April 19, 1994 to brief them on the status of the cases. At that meeting, ORI and NEI staff agreed that a letter would be sent by NEI to all COMS patients regarding the investigations. NEI confirmed that this letter had been sent to every patient by April 29. NEI has also prepared a statement which will be published in the May 18 issue of the Journal of the American Medical Association.

Potential compliance issues concerning the reporting of scientific misconduct to the ORI and the termination of employment prior to an inquiry/investigation remain to be assessed.

B. Inquiry into possible falsification and fabrication of data in the PHS funded ISCHEMIC OPTIC NEUROPATHY DECOMPRESSION TRIAL at Ohio State University (DRI 94-04)

The Ischemic Optic Neuropathy Decompression Trial (IONDT) is another multicenter clinical trial supported by the NEI. The purpose of the trial is to assess the safety and efficacy of optic nerve sheath decompression surgery for non-arteric ischemic optic neuropathy (NAION). NAION is the most common cause of acute optic nerve disease in older persons and causes permanent

and severe visual loss. It is estimated that 6,100 new cases of NAION are seen each year. The IONDT is a randomized clinical trial designed to compare the difference in change in visual acuity at six months in patients assigned to either surgery or careful followup. Begun in November 1992, the trial has 26 participating centers.

On Wednesday April 6, 1994, the Director, IONDT Coordinating Center, University of Maryland at Baltimore, notified the NEI program officer and misconduct officer and also called the Division of Research Investigations (DRI) to report possible misrepresentations of information concerning subjects in the trial provided to the Coordinating Center by members of the project team at Ohio State University (OSU). The IONDT project at OSU has received funding from PHS under a cooperative agreement.

During a December 1993 site visit, numerous protocol violations had been observed and a decision was made to closely monitor the OSU contributions. During the recent site visit (April 4, 1994), the coordinating center staff uncovered discrepancies in information that was provided regarding randomization of subject 027-15 and about subjects' visual acuity measurements at randomization (baseline) which raised the possibility that data had been falsified or fabricated.

From information sent from the Coordinating Center on April 8, 1994, concerning the visual acuity measurements at baseline for some of the OSU patients, DRI indicated to OSU officials that an inquiry would likely be necessary. The Coordinating Center sent DRI a copy of a draft site visit report on the evening of Friday, April 8.

The specific allegations of scientific misconduct as formulated by DRI are that:

1) an individual or individuals at OSU falsified or fabricated information provided to the IONDT Coordinating Center;

2) falsified information regarding randomization of subject #027-15 was reported verbally to Coordinating Center staff during the April 4, 1994, site visit;

3) visual acuity scores of patients randomized to either careful watching or surgery were fabricated or falsified.

DRI requested that OSU conduct an inquiry on April 11, 1994. University of Maryland officials were also notified of this decision because the continuing cooperation of Coordinating Center staff in providing materials, information and possibly technical support would be required.

Mr. DINGELL. Gentlemen, we've kept you here a long time. I want to say a couple things. The NIH is a national treasure and you are guardians of a national treasure. It's one that this committee and the chairman of this subcommittee and this subcommittee, my good friend, Mr. Schaefer, have most actively supported and we intend to continue doing that.

You have had a long and a difficult appearance before the committee. I want to make it very clear to you, Dr. Varmus, and to you, Dr. Broder, that I have immense respect for you both. And I want to make it very clear that I think that the comments that you have made today with regard to the attitude and the behavior of NIH and NCI with regard to scientific misconduct, the protection of participants in trials and tests and research studies that are funded by your agency have been most helpful and are important.

I want you to know that we've long been critical of science and there's been a long effort on the part of this subcommittee to see to it that government money is properly spent, that the protection of participants in trials and tests and studies is adequate, the information available to them is at a level that you and I would like to see them have, and, also, to see to it that the public moneys are well spent and that the factual results of the studies are factually reported, and that there's not misbehavior in terms of fraudulent studies or falsification of data or information and so forth.

It's been a long and hard and difficult task. We found today a new component which is now very clear, and that is it's not just an isolated question in which science will rectify the falsification or the improprieties with regard to data and collection of information, but, rather, that human lives are at stake.

We sense that there is a great awareness on your part, Dr. Varmus and Dr. Broder. I am content to continue to work with you and to watch and see to it that the kind of effort that you are making, which is significantly different and better than your predecessors, including one of your most immediate predecessors, Dr. Varmus, and to see to it that you succeed in your efforts to make this system work better for the benefit of all of us, that the taxpayers' money be better spent, that the protection be afforded to the participants, that the information be such as to give an honest appraisal so that people can make proper judgments with regard to their personal activities, as Ms. Sigal has indicted to us.

So as we close the hearing, I want to express my thanks to you both and also to Dr. Chabner, Dr. Friedman, Dr. Bivens, for your assistance. You've got over there a very nasty job, Doctor, and as for you, Dr. Varmus and Dr. Broder, because occasionally you've got to address the question of scientific behavior within and without the institution and whether or not it conforms with what I think we regard as being the necessary tests. That is that science should be the pursuit of truth and that it should be honestly conducted, with minimal risk and hazard to those who innocently participate in these studies, and that the factual results should be that which add to our knowledge and which increase the safety and the protection of those who pay for it, and that the public money should be properly spent.

I think that you and I look forward to a time when we're going to be able to work better together. If things have happened today

which cause you distress, you have my expression of sorrow and apology.

I want you to understand that we're going to try and work with you. We expect good things from you. We know that you were engaged in a difficult task and, as I've indicated, the communication to the public of potential wrongdoing of a colleague or a scientist, particularly one who might happen to be a famous name or well known and influential figure in science, is always difficult. It's fraught with peril to you, possible lawsuits and other difficulties.

We understand that it takes time to refine the procedures that you have so that you can do this thing properly. We will work with you to get you both the time and a climate in which you may do these things with minimum peril to yourself and greater success from the standpoint of the great undertaking of which you are a part.

So you have our thanks and our good wishes and we will look forward to working with you. We will also look forward to the next hearing in this matter, which will be occurring, I suspect, in the not far future involving the University of Pittsburgh.

Having said those things, we express to you our thanks and our good wishes, gentlemen, and thank you for being with us today.

The subcommittee will stand adjourned till the call of the Chair.

[Whereupon, at 2:15 p.m., the subcommittee adjourned, to reconvene at the call of the Chair.]

[The following letter was received:]

ZENECA
Pharmaceuticals Group

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Wilmington
Delaware 19897 USA

Telephone (302) 886-7751
Fax (302) 886-7688

Alan J. Milbauer
Vice President
External Affairs

April 20, 1994

The Honorable John D. Dingell
Chairman, Subcommittee on Oversight and
Investigations
Committee on Energy and Commerce
Room 2323 Rayburn House Office Building
Washington, D.C. 20515

Dear Mr. Chairman:

I am writing respectfully to request a correction of the record concerning an issue which was raised in the Oversight and Investigations Subcommittee's April 13 hearing on breast cancer research.

In the course of the Subcommittee's hearing, an internal Zeneca memorandum (dated July 7, 1993), which we provided to the Subcommittee, was quoted from and discussed. In questions you asked of Dr. Broder of the National Cancer Institute (NCI), it was implied that this memorandum proved that the NCI had not been notified in a timely way of information Zeneca had received concerning the number of patients within the B-14 trial who were developing endometrial cancer while on NOLVADEX.

This is simply not true. In fact, the memorandum cited in the hearing summarizes a conference call which was held between Dr. Leslie Ford of the NCI, Dr. Fisher of the NSABP and Dr. Paul Plourde of Zeneca to discuss the endometrial cancer issue and the need to modify the label on NOLVADEX. This conference call was initiated by Dr. Plourde as soon as the endometrial cancer information came to his attention. Furthermore, another document we provided to your subcommittee was a copy of a July 8, 1993 letter from Dr. Plourde to Dr. Fisher of the NSABP and Dr. Ford of the NCI. This letter discusses the findings concerning endometrial cancer and Zeneca's proposed amendments to the prescribing information for NOLVADEX. Finally, on June 30, 1993, Zeneca also notified the FDA of these findings and of the proposed labeling changes.

These documents are clear: As soon as Zeneca obtained information concerning the increased incidence of endometrial cancer in the B-14 trial, we alerted the NCI and made appropriate changes to the prescription information for NOLVADEX. In short, Zeneca acted promptly and responsibly.

I appreciate this opportunity to correct the record concerning the unfortunate implication that Zeneca was somehow deficient in reporting information to the NCI. I respectfully request that this letter and the accompanying attachments be entered into the record of the April 13 hearing.

Sincerely,

Alan J. Milbauer
AJM/gfc
Attachments

ZENECA Pharmaceuticals Group

Internal Memorandum

ZENECA, INC.
WILMINGTON, DE 19897
CLINICAL & MEDICAL AFFAIRS
ENDOCRINOLOGY

TO: SEE ATTACHED LISTING

DATE: JULY 7, 1993

FROM: PAUL V. PLOURDE, M.D. CC:

RE: CONVERSATION WITH DR. FISHER (NSABP) & DR. FORD (NCI)

PRIVILEGE AND CONFIDENTIAL: ATTORNEY-CLIENT INFORMATION

Today on July 7, 1993, at 1:30 p.m. I called Dr. Fisher to inform him on the company's position on the association of endometrial cancer with NOLVADEX treatment.

I first discussed with Dr. Fisher that we over the last few weeks have been looking at the association of endometrial cancer with NOLVADEX treatment. This was in part initiated because of the Yale publication reporting that the tumors associated with NOLVADEX treatment were poorly differentiated tumors resulting in a poor prognosis for these patients. Our evaluation from the clinical trial data base as well as from the literature could not confirm this Yale publication. Therefore, we did not feel that we needed to make any changes in our label. However, viligence is necessary and we will continue to monitor this closely. Dr. Fisher thought that this was appropriate and he himself has initiated some activity within the NSABP to explore this further. He is requesting that slides from the endometrial cancer seen in the B-14 trial be evaluated. He plans on doing this over the next several months.

I then proceeded to tell Dr. Fisher that the increasing number of patients within the B-14 trial developing endometrial cancer while on NOLVADEX did prompt us to look at this issue more closely. Upon careful review of the data, we felt that there was an increase risk to develop endometrial cancer with NOLVADEX and that we will modify our label to reflect this. I also commented that it was impossible to precisely quantitate the relative risk although qualitatively it did appear that there was a slight increase incidence. Dr. Fisher agreed with this assessment and felt that we were acting responsible by changing our label. I commented to him that at least in the United States, we would have to make minor changes to our label but I did not see these changes having a great impact on the treatment of patients with confirmed breast cancer and also on the US prevention trial since the protocol did include the B-14 data as well as the Swedish data and that this potential risk was noted on the consent form. However, I did comment that it did have more of an impact on the European trial which would require that the protocol and consent form be modified. Dr. Fisher was told that Dr. Cusick has been notified and the European protocol and consent will be modified.

Dr. Fisher appreciated our willingness to provide him with a copy of the justification document for this label change. Dr. Fisher did comment about the potential negative publicity that could occur. In particular, this could be the bullet being sought by the health authority in the UK to stop the European prevention trial. If that is the case, that would have a major effect in the United States. He agreed that we should be prepared for this potential negative outcome.

I told him that we would be gathering a panel of experts in endometrial cancer together within the next two or three months. This would be an international panel composed of the prevention trial investigators, epidemiologist and gynecologists. Dr. Fisher did not see the great need for having this panel, since he felt that the issue had been examined and he saw no need to rediscuss this issue. However, he understood our desire to convene this panel and agreed to participate.

I also informed him that we did not, as a company, see that the risks had changed appreciably to warrant discontinuation of medication to the NCI. Dr. Fisher was relieved with that decision.

I also informed him of Dr. Cuzick's plan to hold a press conference this coming Friday morning. He was quite surprised about the press conference although he did know that Dr. Cuzick was having an investigators meeting that day. Dr. Cuzick had requested an NSABP representative to attend this meeting. The NSABP due to time constraints, was unable to send anyone and Dr. Cuzick then called Dr. Ford at the NCI and it was agreed that Dr. Susan Nayfield from the NCI was to represent the US. Dr. Fisher and Dr. Ford were unaware that a press conference was going to be held.

I told Dr. Fisher that I wanted to call the NCI and inform him of these changes. He insisted that he call Dr. Ford to discuss the issues, but finally he agreed to have a conference call with Dr. Ford.

Later this same day, a conference call was held between Dr. Leslie Ford from the NCI and Dr. Fisher from the NSABP. Dr. Fisher had briefed Dr. Ford on the issues that we had discussed above. Dr. Ford had no comments and agreed with our approach in regards to the label change. She did not feel that, the US needed to make any changes in the consent form or the protocol since the endometrial cancer issue that had already had been addressed consistant with our new label change. She recognized however, that this could cause some unnecessary and inappropriate publicity. With this, Dr. Ford did have concerns about Dr. Nayfield being in the UK during the press conference and the meeting. She will be contacting Dr. Nayfield to alert her of our intention to modify our label. Dr. Nayfield will be instructed not to participate in the press conference.

Dr. Ford also told me that the MRC had recently approved the protocol this week. This needs to be confirmed, but if true, this would minimize the impact of Cuzick's press conference. (i.e., the UK Health Authority may not be in a position to be embarrassed as was originally feared).

I discussed the panel of experts to be organized to review the data. Both felt that this was unnecessary. She informed me that as far the Prevention Trial, a sub-study will be conducted where endometrial sampling will be done periodically during the trial.

I told Drs. Ford and Fisher that I would be sending them a copy of the justification document and that they should hold this document as confidential information. I also informed them that I would be glad to send them a copy of the specific wording change we are recommending as a label change for their information.

Overall, this interaction was positive and I believe that both groups felt happy that we were keeping them informed.

PVP:mc

ZENECA
Pharmaceuticals Group

1800 Concord
Wilmington
Delaware 19897 USA

July 8, 1993

Bernard Fisher, M.D.
University of Pittsburgh
School of Medicine
914 Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15261

Leslie Ford, M.D.
National Cancer Institute
Room 300
Executive Plaza North
Bethesda, MD 20892

Dear Drs. Fisher and Ford:

Further to our telephone conversation last week, I enclose a copy of the report which ve have prepared for discussion vith regulatory authorities to support our proposal to amend the prescribing information for NOLVADEX vith respect to endometrial changes, vith particular reference to endometrial cancer. Although I assume that you will vish to discuss the contents of the report with your clinical colleagues of the NSABP and NCI, it is a condition of this disclosure to you that the Groups treat the data as confidential and does not disclose the contents of the report to any third party.

ZENECA Pharmaceuticals believe that the information currently available strengthens the association between NOLVADEX and an increased incidence of endometrial cancer, and that this does therefore impact on the assessment of the risk benefit ratio for women participating in the current prevention trials.

We are therefore informing all 3 groups (US, Italy in addition to UK) of this information as one of the conditions governing our agreement to supply clinical trial medication i.e. that ve would inform the groups of any significant information relevant to tamoxifen as and vhen it became available during the course of the studies. In turn ve require that each group nov ensures that this increased risk is appropriately reflected in the trial protocol and consent form and that adequate measures are in place for monitoring the occurrence of endometrial changes during the trial.

Although the NSABP P1 protocol and consent form does address this issue, I vould ask that you, upon reviev of this document, re-examine if both the protocol or consent form needs to be amended.

I must remind you that the continued supply of trial medication to the NCI depends upon the adoption of these measures.

As I mentioned on the phone, we believe that it would be appropriate to convene a workshop involving not only representatives of the 3 prevention trials but also a number of independent experts in the fields of epidemiology, breast cancer and gynecology, so that we can discuss together the impact of the information available on risk-benefit assessment for women participating in these trials. We will be progressing this over the next 2-3 months. In the meantime, obviously we felt it very important that you see this information.

Best regards.

Sincerely,

Paul V. Plourde, M.D.
Director, Endocrine Research

PVP:mc

INTERNAL MEMORANDUM

ZENECA Pharmaceuticals Group
Drug Regulatory Affairs
Telephone (302)886-2127

DATE: 30-Jun-1993 10:50am EDT

TO: See Below

FROM: Anthony F. Rogers

SUBJECT: FDA CONTACT-NOLVADEX

AT 10:20 TODAY I CONTACTED MR. PAUL ZIMMERMAN (FDA-CSO) TO ADVISE HIM OF THE FOLLOVING:

1-DES ISSUE: ZENECA IS PREPARING A DOCUMENT WHICH PROVIDES ALTERNATIVE LANGUAGE AND JUSTIFICATION. THIS DOCUMENT WILL BE AVAILABLE LATE NEXT VEEK AND I WILL CALL HIM WHEN I RECIEVE IT. HE AGREED.

2-ENDO CHANGES: BASED ON CURRENT REVIEV OF DATA ZENECA WILL MODIFY THE PIB TO UPDATE THE LANGUAGE DESCRIBING ENDOMETRIAL CHANGES. HE ASK FOR THE LANGUAGE AND I READ TO HIM THE PROPOSED EID STRESSING THAT IT VAS DRAFT AND COULD CHANGE BUT THE MESSAGE VOULD NOT. I ALSO STATED THAT DR. FLOURDE VILL CALL DR. FISHER LATER IN THE DAY TO ADIVSE HIM OF THE LABEL CHANGE. HE ASKED IF ANYTHING VILL CHANGE REGARDING THE PREVENTION TRIAL. I SAID THAT OUR POSITION IS THAT THE RISK/BENEFIT RATIO FOR BREAST CANCER TREATMENT DOES NOT CHANGE AND THAT THE PREVENTION TRIAL SHOULD CONTINUE BUT THAT VAS DR. FISHER'S DECISION. VE BELIEVE THAT THE ISSUE OF ENDOMETRIAL FINDINGS OPPOSITE NOLVADEX TREATMENT HAVE BEEN PROPERLY ASSESSED IN THE DELIBERATIONS REGARDING THE PREVENTION TRIAL AND THAT THE LABEL CHANGE STRENGHTENS THE LANGUAGE IN THE PIB. HE ASKED IF ZENECA VAS GOING TO DO ANYTHING FURTHER REGARDING THIS ISSUE. I ADVISED THAT IN THE NEAR FUTURE VE VILL CONVENE A PANEL OF EXPERTS TO REVIEV THE DATA AND THAT I VILL ADVISE FDA VHEN THIS VILL TAKE PLACE. HE SAID THAT HE VILL ADVISE DR. JUSTICE (FDA-MEDICAL REVIEVER) OF THE LABEL CHANGE. I TOLD MR. Z THAT IF FDA NEEDED ANYMORE INFO TO CONTACT ME. HE AGREED.

TONY

Distribution:

TO: Jack G. Duncan
Jim O'Shea
Donald R. Ward
Orlando Ceaser
Jeffrey A. Soper
Steven B. Lampert
Rebecca D. Cintron, M.D.
* Paul V. Plourde
Karen R. Lines
William C. Lucas
William J. Kennedy
Hamish Cameron
Jenny Holmes
Ronald L. Krall

SCIENTIFIC MISCONDUCT IN BREAST CANCER RESEARCH

WEDNESDAY, JUNE 15, 1994

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2123, Rayburn House Office Building, Hon. John D. Dingell (chairman) presiding.

Mr. DINGELL. The subcommittee will come to order.

In April of this year, the subcommittee held a hearing on a series of issues involving the University of Pittsburgh's and Dr. Bernard Fisher's mismanagement of and the National Cancer Institute's failure to oversee, some of the Nation's most important clinical trials involving the treatment and prevention of breast cancer. Some of the issues discussed at that hearing included the falsification and fabrication of data at St. Luc Hospital in Montreal, Canada; the failure of the University of Pittsburgh, Dr. Fisher, and NCI to deal with the fraud in a timely manner; the failure of Dr. Fisher, NCI, and the Office of Research Integrity (ORI) to inform the women of America of the fraud for nearly 3 years; Dr. Fisher's failure to publish a reanalysis of the data, which was required to be done because of the need to exclude the fraudulent St. Luc data excluded; the failure of Dr. Fisher to inform NCI, Zeneca, which is the pharmaceutical manufacturer of tamoxifen, and the American women in a timely manner about the endometrial cancer deaths due to tamoxifen; and the failure of Dr. Fisher and his colleagues to inform NCI about audit findings revealing significant data irregularities at a second Montreal hospital, St. Mary's.

These multiple and serious failings came to a head in March of this year, when the media broke the news and the American public finally learned what NCI, the University of Pittsburgh, and Dr. Fisher should have told them long ago. And yet, these revelations are only a part of a long story.

First, new problems have been disclosed at several additional sites. In March 1994, NCI found reports of audits conducted in November 1992 at Tulane and LSU. These National Surgical Adjuvant Breast and Bowel Project reports, that is, NSABP reports, prepared one year following the audits, revealed serious and chronic problems of missing and misrepresented data. In fact, the majority of the data at these two sites could not be located.

After two further NCI audits at these two sites, significant questions remained about the completeness and the accuracy of the data. And the audit process continues.

In two other instances, the subcommittee identified audit reports, one dating from 1990 and one from 1992, both of which revealed very significant discrepancies and irregularities. At Memorial Cancer Research Foundation, the NSABP auditor reported, among numerous other items, that, "A serious problem has been identified with this institution with respect to the accuracy of the data reported to the NSABP at the time of randomization." Further, the NSABP audit report cited a "serious problem" at the site because, and I quote again, "IRB, Institutional Review Board, will not approve or reapprove the NSABP protocols."

At South Nassau Communities Hospital, two of eight patients reported as eligible were found by the audit to be clearly ineligible due to their medical history. The auditor recommended, and I quote, "additional randomization be suspended from this institution until such time as the principal investigator and his associates develop procedures which ensure eligibility, treatment, and follow-up of all patients entered into NSABP protocols."

Curiously, neither of these problem-ridden audits received any effective follow-up. Indeed, in the case of the Memorial Cancer Research Foundation, the original audit report was found in a file drawer at Pittsburgh. The report had never been sent to NCI or to the research site.

The NCI recently completed an audit at the Foundation, and as a result, NCI has referred the site for formal investigations of scientific misconduct and violation of Department of Health and Human Services regulations for the protection of human research subjects.

As for South Nassau, contrary to NSABP's claims to NCI, it was not suspended. No effort has been made to determine how widespread the observed discrepancies were. Neither was any effort made to determine if patients had been harmed by their entry into protocols for which they were not eligible. Further reviews of South Nassau are now pending.

Moreover, the subcommittee's review of hundreds of audit reports revealed that, in many cases, NSABP was years behind in performing audits and in writing up and forwarding audit reports after the audits were completed. More significantly, the follow-up to identified audit deficiencies was all but nonexistent.

NSABP itself has recently begun to review its own past audits and reported several dozen sites with major discrepancies that have not been resolved yet. Dr. Fisher and his colleagues have claimed this was due to a lack of resources for an adequate audit staff. They claimed that they asked for additional resources from NCI, but were turned down. NCI says that this is not so.

The revelations prior to and at the April hearing, as well as subsequently, have triggered a number of further developments:

Dr. Fisher has been removed as head of NSABP;

Some of Dr. Fisher's top colleagues at the University of Pittsburgh, under the cloak of anonymity, started what appears to have been an ill-advised letter-writing campaign. They were demanding an investigation of the NCI Director, Dr. Samuel Broder, and the

reinstatement of Dr. Fisher, even in the face of mounting evidence of significant management failures;

At the recommendation of NCI, the Office of Research Integrity has directed Pittsburgh to conduct an inquiry to determine if a scientific misconduct investigation is warranted involving the actions of Dr. Fisher and others at NSABP;

And the grant for the overall administration of NSABP will be recompeted next year.

The senior vice chancellor for health sciences at the University of Pittsburgh told the subcommittee staff he believes there is a culture in the scientific community of inappropriate deference to the superstars of science. He believes that this culture has resulted in numerous institutions failing to carry out their lawful responsibilities in overseeing the work and actions of prominent scientists. The University of Pittsburgh now says that this culture of deference was a significant factor in its failure to oversee the work of Dr. Fisher.

This same problem has become apparent to a number of other institutions and has been found in a number of other questions examined by this subcommittee. We hope that the scientific community as a whole will come to recognize that this is a serious problem.

Second, for years there have been questions about the role of pharmaceutical company funds in clinical research. Here, very substantial sums of money, with little or no accounting for the expenditure of that money, passed from Zeneca to NSABP, and to the University of Pittsburgh. It will be noted that a precise accounting has not been obtained from any of the parties.

In turn, the manufacturer gained substantial benefits via eventual food and drug approvals, publicity, and similar events. The estimated figures show that Zeneca gave the University of Pittsburgh some $600,000 for a chair for Dr. Fisher. Zeneca also gave NSABP about $600,000 for their semiannual meetings. Zeneca also supplied to NSABP about $300,000 for other purposes. This is a total of over $1.5 million, plus the substantial cost of supplying the tamoxifen drug free of charge for the trials.

Essentially, at the same time the audit program was floundering, Zeneca was providing huge sums of money, not for audit resources, but for lavish parties and receptions at NSABP's semiannual meetings. These meetings were held in splendid places around the United States and Canada. For example, the meetings were in places which imposed severe hardship on attendees such as the Doral Country Club; Banff Springs Hotel in the Canadian Rockies; Chateau Frontenac in Quebec City; the Fairmont Hotel in San Francisco; Hilton Head, S.C.; Vancouver, British Columbia; Palm Springs, Calif.; DisneyWorld and Bal Harbour, Fl.

Some of the receptions included, among other things, strolling troubadours, wine-tasting parties, fire dances, live steel bands, and fine food, champagne, and dance. At Bal Harbour, they touted an elegant evening at the seashore with premium hard liquor, beer, and wine. A number of these receptions cost up to $80,000 apiece. Curiously, in 1991, the entire NSABP audit function was carried out on a budget of a little more than $80,000.

Third, today we will hear about the failure to report in a timely manner the deaths from endometrial cancer of patients receiving tamoxifen in Dr. Fisher's studies. We will also examine the matter of informed consent for the tamoxifen prevention study. While this study was in progress and after Dr. Fisher and his colleagues learned of at least two deaths in the study, deaths ultimately proven to be due to endometrial cancer, a sentence was added to the informed consent that said, and I quote now, "No deaths from endometrial cancer have been reported." This sentence was not removed from the consent form until 1994, at which time Dr. Fisher had learned of the death of at least four persons related to endometrial cancer.

We look forward to hearing Dr. Fisher's account and explanation of these matters.

In concluding the opening statement, the Chair wants to remind all of us of what is most important in this affair. This matter is part about failed responsibility. It is part about failures of scientific integrity. But above all, the question that should concern us most is the welfare of the thousands of women who, at some considerable risk to themselves, committed their lives and health to these studies.

The fact that thousands of women were involved, the fact that statistical power was so great that, overall, the conclusions may not be changed, does not mitigate the sacrifice of the women who were entered into studies for which they were not eligible or for which they did not give consent or on which they were not properly informed. It does not compensate for the risks these women faced, only to have their data discarded due to abject sloppiness, gross negligence or even fraud.

As we proceed today, the Chair reminds us all that it behooves us to be mindful of, and to honor, these women.

The Chair recognizes the gentleman from Ohio.

Mr. BROWN. Thank you, Mr. Chairman. I want to thank you again for holding this follow-up hearing on scientific fraud in federally funded breast cancer research. It is obviously an important issue that warrants this subcommittee's and this Congress's immediate attention.

What is it we are really talking about today? We are talking about the health and well-being of our wives, our mothers, our daughters. Women all over America are doubting their choices and questioning their health decisions. We owe it to them to give them answers on which they can depend.

Unfortunately, we are currently stuck in a holding pattern. With each new audit, it appears there is new information about bad or missing data, about inappropriate enrollment of women in the study, about inaccurate reporting and follow-up. In a study of this magnitude, at some point you are likely to encounter a few simple errors in the collection of information. However, the extent to which there have been errors and to which there have been false data uncovered is alarming; and I believe it calls for complete investigation.

In addition, it is clear that NSABP has been quite lax in its own auditing to ensure clean and useful information.

Mr. Chairman, I don't believe that any of us wants to bring down the scientific establishment or damage the reputation of NSABP. At the same time, we owe it to all women to ensure that the information they use in consultation with their physicians is truthful, is reliable, and is up to date.

Thank you, Mr. Chairman.

Mr. DINGELL. The time of the gentleman has expired.

The Chair recognizes now the distinguished gentleman from Colorado, the Ranking Minority Member of the committee, for such opening statement as he chooses.

Mr. SCHAEFER. Thank you, Mr. Chairman. As the subcommittee and the chairman know, I began our April hearing on this matter by stating that we must seek to reassure the American people about the soundness of American science. Two months have passed, and although we have made some progress towards this goal, we still have a lot to accomplish.

Thanks to your leadership, Mr. Chairman, this subcommittee acted promptly in exploring the circumstances surrounding research activities of the NSABP. It did so in a calm, professional manner because, while it is vital that we uncover fraud and mismanagement, it is also essential that we calm the fears of American women who relied on the studies in this question.

We are relieved to learn that the basic results of the study containing falsified data have since been verified by subsequent analysis. I am troubled, however, to find that the problems outlined at our April hearing were more the rule rather than the exception.

The subcommittee staff has done a terrific job in uncovering these problems. It has learned that extensive reporting problems across the United States and Canada existed. The NSABP did send competent and able auditors into the field, it seems. However, it failed to act upon the information received from its audit teams, neither generating appropriate reports nor notifying the institutions of potential problems.

This situation was unacceptable in April and it certainly is today. The Food and Drug Administration and the NCI have allowed breast cancer prevention trials to resume; and while I agree this research is definitely important, given the track record of NSABP, I have very, very serious concerns.

Now, Mr. Chairman, I look forward to hearing what actions have been taken by the University of Pittsburgh since our last hearing, as well as learning what the National Cancer Institute has done in light of the testimony this subcommittee received.

This hearing is not about an institution or research program, it is about millions of American women who have a right to be able to rely on scientific and medical information given to them by their government; and that is why these hearings are so important, Mr. Chairman. I certainly applaud you for continuing this effort.

Yield back.

Mr. DINGELL. The Chair thanks the gentleman.

The Chair wants to observe that the staffs of the Minority and the subcommittee have worked very closely on this matter, as they always do, and I want to express my appreciation to my friend from Colorado and to his very able staff for their assistance in this matter.

The gentlewoman from Pennsylvania.

Ms. MARGOLIES-MEZVINSKY. Thank you, Mr. Chairman, thank you for having these hearings and continuing to do so.

Mr. Chairman, I would like to thank you for all that you have done with regard to the National Surgical Adjuvant Breast Project. The NSABP is an important, federally funded program which was designed to study treatments for breast cancer and bowel cancer, as we know. I am pleased that we will be hearing from several important witnesses today regarding their role in the recently discovered auditing problems with the program.

The question on all women's minds is whether the conclusions of these studies should be trusted. I want to make sure that we can assure women across this country that underlying recommendations for treatment of breast cancer have not changed. Instead, this hearing will focus on problems with breast cancer programs and will ensure that in the future such mistakes will not be made again.

I think that we have some fundamental questions that must be answered, and I hope that they will be answered here today; that is, how did it happen, how can we prevent this from happening again, how can we in general be more vigilant, and how can we answer questions for folks like Jill Sigal, who is in the audience here today, when she asked, can women who choose lumpectomy over mastectomy be comfortable with their decisions?

I look forward to hearing from the panel. Thank you once again, Mr. Chairman, for holding these hearings.

[The opening statement of Ms. Margolies-Mezvinsky follows:]

STATEMENT OF HON. MARJORIE MARGOLIES-MEZVINSKY

Mr. Chairman, I would like to thank you for holding this second hearing on the National Surgical Adjuvant Breast Project (NSABP). The NSABP is an important Federal funding program which was designed to study treatments for breast cancer and bowel cancer. I am pleased that we will hear from several important witnesses today regarding their role in the recently discovered auditing problems with the program.

The question on all women's minds is whether the conclusions of these studies should be trusted. I want to assure women across America that the underlying recommendations for treatment of breast cancer have not changed. Instead, this hearing will focus on problems with breast cancer program and will ensure that, in the future, such mistakes will not be made again.

I am pleased that there will four panels testifying today, including representatives from Zeneca Pharmaceuticals, Dr. Bernard Fisher, the former director of NSABP, representatives from the University of Pittsburgh, and Dr. Samuel Broder, Director of the National Cancer Institute.

In the past few months, we have heard press accounts of several serious auditing problems with certain sites in these studies. These auditing problems seem to be pervasive in certain sites of the study. I am disturbed that the information about faulty data was not shared with the National Cancer Institute in a more timely manner. I understand that new procedures have been put into place to ensure that this detections of faulty data will be given to both the National Cancer Institute, the NSABP, and officials with Zeneca. All parties must be fully informed of any problems to ensure that women can trust the result of these trials.

In addition, I am pleased that the National Cancer Institute is conducting its own auditing procedures to determine if further problems there are in the NSABP. These confirmations of previous auditing are necessary to ensure the soundness of the conclusions of clinical trials.

Finally, I am pleased that the clinical preventive trials on tamoxifen have been restarted. Many women are interested in the results of these preventive trials. I believe that the Congress must continue to be vigilant to ensure that proper auditing standards are being applied to all clinical sites. It is my understanding that a new

auditing system will be used in these preventive trials to ensure that all women in these trials have been given a consent form, that their clinical information has been confirmed, and that proper precautions are being taken to prevent further abuses in this vital research project.

I look forward to learning more about this situation and will continue to be vigilant in my efforts to assert the facts regarding this research project. The women of America deserve to know the facts, and I will make sure that those facts are available to them.

Mr. DINGELL. The Chair thanks the gentlewoman for her opening statement.

The Chair announces that the first panel will be composed of Dr. John Patterson, M.D., international medical director, Zeneca Pharmaceuticals Group, accompanied by Dr. Paul Plourde, senior director, clinical and medical affairs, Zeneca Pharmaceuticals Group, and Alan Milbauer, vice president, external affairs, Zeneca Pharmaceuticals Group.

Gentlemen, welcome to the subcommittee.

Gentlemen, as you are no doubt aware, it is the practice of this subcommittee that all witnesses testify under oath. Do any of you object to so doing?

The Chair advises that, given the fact that you are testifying under oath, it is your right to be advised by counsel. Do any of you desire to be advised by counsel during your appearance here?

Very well, then gentlemen for your information, copies of the rules of the committee, the subcommittee and the House of Representatives are there in the red and the blue booklets before you at the table.

Gentlemen, if you have no objection, then, to testifying under oath, would you please each rise and raise your right hand.

[Witnesses sworn.]

Mr. DINGELL. Gentlemen, you may each consider yourself under oath. We will recognize you starting with Dr. Patterson; then, Dr. Plourde and Mr. Milbauer, you will be recognized for such statements as you choose to give. Gentlemen, proceed.

TESTIMONY OF JOHN PATTERSON, INTERNATIONAL MEDICAL DIRECTOR, ZENECA PHARMACEUTICALS GROUP, ACCOMPANIED BY PAUL PLOURDE, SENIOR DIRECTOR, CLINICAL AND MEDICAL AFFAIRS, AND ALAN MILBAUER, VICE PRESIDENT, EXTERNAL AFFAIRS

Mr. PATTERSON. Thank you, Mr. Chairman. Mr. Chairman and members of the subcommittee, I am Dr. John Patterson, international medical director of Zeneca Pharmaceuticals, working at our company's headquarters in the United Kingdom. Joining me today are Dr. Paul Plourde, senior director of clinical and medical affairs, and Alan Milbauer, vice president, external affairs, at Zeneca Pharmaceuticals Group, both based in Wilmington, Delaware. Zeneca is a bioscience-based business, formerly a part of Imperial Chemical Industries, or ICI.

Our company is proud of its history of dedication to scientific research and patient support in the field of women's health. Zeneca is the discoverer, developer and manufacturer of Nolvadex, the world's leading drug for the treatment of breast cancer and the world's most prescribed anticancer medicine. Nolvadex is our trade name for tamoxifen. Since 1973, millions of patients have taken

tamoxifen as an important component of their breast cancer treatment.

In recent months, there has been considerable press regarding tainted data in breast cancer trials conducted by NSABP. It is understandable that patients are wondering if the medical basis for choosing their treatment is correct. They have also heard that the risk of developing uterine cancer as a side effect of treatment with tamoxifen is greater than previously thought, and they wonder how that risk applies to them. Additionally, they have witnessed a heated public debate over the merits of the use of tamoxifen to prevent breast cancer in healthy women who are at high risk of developing this deadly disease.

We are concerned that public confusion over these issues could lead patients with breast cancer to be afraid of tamoxifen, a medication with the demonstrated ability to delay recurrence of their disease and prolong their lives.

Mr. Chairman and members of the subcommittee, let me be very clear: For treatment of breast cancer, tamoxifen is one of the most studied drugs in the world. Its safety and efficacy for this purpose is very well established. With over 6 million patient-years of experience in more than 20 years of clinical use around the world, tamoxifen continues to be a key weapon in the battle against breast cancer.

In patients with early-stage breast cancer, tamoxifen reduces the risk of recurrence of the disease after 10 years by up to ⅓, and it reduces the odds of death by 20 percent. Further, clinical trials of patients with early breast cancer have also demonstrated a marked reduction in new cancers affecting the other breast in women treated with tamoxifen.

In summary, the proven benefits of tamoxifen in the treatment of breast cancer in men and women outweigh its risks. It is my hope that these hearings will underscore this indisputable fact.

As an anticancer agent, tamoxifen is a powerful medicine, and in recent years, an increased risk of developing uterine cancer has been reported in women who are taking it. Zeneca has closely monitored the incidence of uterine cancers, both from clinical trials and spontaneous reports. We have promptly reported the data to the FDA and have also presented it to independent experts for evaluation.

Starting in 1989, Zeneca has amended its U.S. label on four different occasions as new information about the risk of uterine cancer was received. We have recent data collected from 14 studies involving nearly 17,000 women worldwide. They indicate that the increased risk of uterine cancer associated with tamoxifen is approximately 20 times smaller than the more deadly risk that breast cancer will recur or spread if patients do not take tamoxifen.

Much has been made in the press about reports of uterine cancer deaths in the large B-14 trial involving tamoxifen in breast cancer patients being conducted by NSABP. To obtain accurate, long-term information, the women who participate in this trial are followed until they die. Thus, reports of deaths are an expected component of cancer clinical trials; and it is a sad fact, Mr. Chairman, that even with a potentially curable tumor such as uterine cancer, some women contracting this cancer will die of it.

We have been informed that one of the subjects of today's hearing will be the timeliness of reports about four uterine cancer deaths that occurred in the B-14 trial. The first of those deaths occurred on June 25, 1991. Zeneca was informed of that death on February 10, 1992, in a routine NSABP report. The cause of death was not clearly stated, and several potential causes were listed which included uterine cancer.

We reported this case to the Food and Drug Administration on April 1, 1992. NSABP reported the remaining three uterine cancer deaths to Zeneca on December 13, 1993, and we reported these to FDA on January 5, 1994. According to the subcommittee staff, the NSABP apparently has claimed that it notified Zeneca of one of these deaths on February 1, 1993.

In fact, NSABP provided Zeneca with a large data set, including data that reflected that death, but no cause of death was specified in that data. It was not until December 1993 that Zeneca learned from NSABP that this death was, in fact, due to uterine cancer. Indeed, NSABP's own August 1993 report to its membership failed to identify any uterine cancer death in any patient.

The B-14 uterine cancer deaths have brought into question the wisdom of continuing tamoxifen in the prevention trial. I want to make it clear to this committee that Zeneca is not sponsoring or endorsing the tamoxifen breast cancer prevention trial. This trial is sponsored by the National Cancer Institute and is being conducted by NSABP. A brief history of the genesis of the prevention trial may be helpful to the committee.

In 1985, Zeneca was strongly encouraged by a significant number of scientists in the medical community to sponsor a tamoxifen breast cancer prevention trial. We responded by organizing a conference involving leading experts in medical oncology, animal toxicology, and epidemiology. The consensus was that additional data were required before an informed decision could be made on the appropriateness of the prevention trial. As additional data became available, Zeneca provided it both to regulatory authorities and the scientific community.

In 1990, members of the academic community again approached Zeneca about a possible prevention trial. The company reiterated its concerns. However, following many discussions, the National Cancer Institute, the FDA, and medical experts decided that the potential risks and benefits put together—that the benefits outweighed the risks and that a study of tamoxifen in prevention should be conducted.

Zeneca, then the sole supplier of tamoxifen in the United States, subsequently agreed, at NCI's request, to provide tamoxifen tablets and matching placebo for the study. The tablets were supplied free of charge on the understanding that participants were to be properly monitored and fully informed of the potential risks. NSABP also agreed to notify Zeneca of any significant new findings in the study.

We have been informed that another subject of today's hearing will be Zeneca's financial relationships with the University of Pittsburgh and the NSABP. Let me assure you, Mr. Chairman, that our relationship with the University and NSABP was at all times proper and consistent with applicable legal, ethical, and moral stand-

ards. Any insinuation to the contrary is completely false. I have outlined the full extent of these relationships in my written statement to the subcommittee.

In summary, payments were made by Zeneca to NSABP for three categories of work; namely, data processing and management, support for meetings, activities, and honoraria and travel costs to Drs. Fisher and Redmond in respective appearances at FDA and scientific meetings. In addition, Zeneca agreed to partly fund, at the request of the University of Pittsburgh, a chair in the Department of Surgery at Pittsburgh. Zeneca's conduct in this respect was entirely consistent with both the spirit and letter of FDA policy and the codes of conduct adopted by the American Medical Association and the Pharmaceutical Research Manufacturers Association, not to mention our own internal corporate guidelines, as they applied then and as they apply now.

We believe that our financial assistance to the University of Pittsburgh and NSABP contributed to breast cancer research in the United States and fostered a better understanding of breast cancer treatment around the world. We do not believe that this financial support caused NSABP to be less diligent in reporting safety information regarding tamoxifen. In fact, much of our financial support was given specifically to obtain extra safety reports to submit to the Food and Drug Administration and to facilitate the exchange of information amongst breast cancer researchers.

In conclusion, Mr. Chairman, we at Zeneca are committed to the development and support of safe medicines backed by good science and proper scientific practices. We believe that tamoxifen is a safe and effective medicine vital to the treatment of breast cancer. We deplore fraud and poor scientific practices in clinical research. We accordingly are pleased to assist the subcommittee in this investigation.

Thank you for the opportunity to speak. My colleagues and I would now be happy to answer your questions.

[The prepared statement of Dr. Patterson follows:]

STATEMENT OF JOHN PATTERSON

Mr. Chairman and Members of the Subcommittee, I am Dr. John Patterson, International Medical Director of Zeneca Pharmaceuticals, working at our company's headquarters in the United Kingdom. Joining me today are Dr. Paul Plourde, Senior Director of Clinical and Medical Affairs, and Alan Milbauer, Vice President External Affairs at Zeneca Pharmaceuticals Group, both based in Wilmington, Delaware. Zeneca is a bioscience based business, formerly a part of Imperial Chemical Industries, or ICI.

Our company is proud of its history of dedication to scientific research and patient support in the field of women's health. Zeneca is the discoverer, developer and manufacturer of Nolvadex, the world's leading drug for the treatment of breast cancer and the world's most prescribed anticancer medicine. Nolvadex is our trade name for tamoxifen. Since 1973, millions of patients have taken tamoxifen as an important component of their breast cancer treatment.

In recent months, there has been considerable press regarding tainted data in breast cancer clinical trials conducted by NSABP. It is understandable that patients are wondering if the medical basis for choosing their treatment is correct. They have also heard that the risk of developing uterine cancer as a side effect of treatment with tamoxifen is greater than was previously thought, and they wonder how this risk applies to them. Additionally, they have witnessed a heated public debate over the merits of the use of tamoxifen to prevent breast cancer in healthy women who are at high risk of developing this deadly disease. We are concerned that public confusion over these issues could lead patients with breast cancer to

be afraid of tamoxifen, a medication with the demonstrated ability to delay recurrence of their disease and prolong their lives.

Mr. Chairman and Members of the Subcommittee, let me be very clear: For treatment of breast cancer, tamoxifen is one of the most studied drugs in the world. Its safety and efficacy for this purpose are very well established. With over six million patient-years of experience in more than 20 years of clinical use around the world, tamoxifen continues to be a key weapon in the battle against breast cancer. In patients with early stage breast cancer, tamoxifen reduces the risk of recurrence of the disease after 10 years by up to one third, and reduces the odds of death by 20%. Further, clinical trials of patients with early breast cancer have also demonstrated a marked reduction in new cancers affecting the other breast in women treated with tamoxifen. Data also suggest that tamoxifen may decrease cardiovascular disease and stabilize postmenopausal bone loss. In summary, the proven benefits of tamoxifen in the treatment of breast cancer in men and women outweigh its risks. It is my hope that these hearings will underscore this indisputable fact.

As an anticancer agent, tamoxifen is a powerful medicine and, in recent years, an increased risk of developing uterine cancer has been reported in women who are taking it. Zeneca has closely monitored the incidence of uterine cancers both from clinical trials and spontaneous reports. We have promptly reported that data to the FDA and have also presented it to independent experts for evaluation. Starting in 1989, Zeneca has amended its label on four different occasions as new information about the risk of uterine cancer was received. We have recent data collected from 14 studies involving nearly 17,000 women. They indicate that the increased risk of uterine cancer associated with tamoxifen is

approximately 20 times smaller than the more deadly risk that breast cancer will recur or spread if patients do not take tamoxifen.

Much has been made in the press about reports of uterine cancer deaths in the large B-14 trial involving tamoxifen in breast cancer patients that is being conducted by NSABP. To obtain accurate, long-term information, the women who participate in this trial are followed until they die. Thus, reports of deaths are an expected component of cancer clinical trials, and it is a sad fact that, even with a potentially curable tumor such as uterine cancer, some women contracting this cancer will die.

We have been informed that one of the subjects of today's hearing will be the timeliness of reports about four uterine cancer deaths that occurred in the B-14 trial. The first of those deaths occurred on June 25, 1991. Zeneca was informed of that death on February 10, 1992 in a routine NSABP report. The cause of death was not clearly stated and several potential causes were listed including uterine cancer. We reported this case to the FDA on April 1, 1992. NSABP reported the remaining three uterine cancer deaths to Zeneca on December 13, 1993. We reported these deaths to the FDA on January 5, 1994. According to the Subcommittee staff, the NSABP apparently has claimed that it notified Zeneca of one of these deaths on February 1, 1993. In fact, NSABP provided Zeneca with a data set reflecting that death, but no cause of death was specified. It was not until December 1993 that Zeneca learned from NSABP that this death was due to uterine cancer. Indeed, NSABP's own August 1993 report failed to identify any uterine cancer death in any patient.

The B-14 uterine cancer deaths have brought into question the wisdom of continuing the tamoxifen prevention trial. I want to make it clear that Zeneca is not sponsoring or

endorsing the tamoxifen breast cancer prevention trial. This trial is sponsored by the National Cancer Institute (NCI) and is being conducted by NSABP. A brief history of the genesis of the prevention trial may be helpful:

In 1985, Zeneca was strongly encouraged by a significant number of scientists in the medical community to sponsor a tamoxifen breast cancer prevention trial. Zeneca responded by organizing a conference involving leading experts in medical oncology, animal toxicology and epidemiology. The consensus was that additional data were required before an informed decision could be made on the appropriateness of a prevention trial.

As additional data became available, Zeneca provided it to regulatory authorities and the scientific community. In 1990, members of the academic community approached Zeneca again about a possible prevention trial. The company reiterated its concerns. Following many discussions, the NCI, the FDA and medical experts decided that the potential benefits of prevention outweighed the risks and that a study of tamoxifen in prevention should be conducted.

Zeneca, then the sole supplier of tamoxifen in the United States, subsequently agreed, at NCI's request, to provide tamoxifen tablets and matching placebo for the study. The tablets were supplied free of charge on the understanding that participants were to be properly monitored and fully informed of the potential risks. NSABP agreed to notify Zeneca of any significant new findings.

As a company, Zeneca has a major commitment to research not only on breast cancer but also on other conditions that affect women's health. We have participated and will continue to participate in all appropriate discussions of the scientific issues and facts that

have a bearing on the prevention and treatment of breast cancer.

We have been informed that another subject of today's hearing will be Zeneca's relationship with the University of Pittsburgh and the NSABP. Let me assure you that our relationship with the University and the NSABP was at all times proper and consistent with applicable legal, ethical and moral standards. Any insinuation to the contrary is completely false. I would like to outline for the Subcommittee the full extent of these relationships.

Zeneca first developed a working relationship with NSABP in the mid-1970's, after tamoxifen had been approved for use in the U.K. but before it had been introduced in the United States. When NSABP approached us regarding the use of tamoxifen in trials, they were one of the leading breast cancer research groups in the world, with an unequalled reputation for conducting large scale cancer clinical trials.

Over these nearly twenty years, the NSABP has conducted a large number of trials on tamoxifen, all of which were developed, funded, approved and conducted under the auspices of the NCI. With the exception of the prevention trial, all previous NSABP tamoxifen studies have been undertaken with large groups of women who have been diagnosed and treated surgically for breast cancer.

Starting in 1982, we contracted with the NSABP to obtain data from the trials they were conducting on tamoxifen. These data were used to support our applications to the FDA for new indications for tamoxifen and to comply with FDA safety and monitoring requirements. Since 1982, payments from Zeneca to NSABP for the cost associated with data management, analyses and reports on studies of tamoxifen have totaled approximately $200,000. An additional $73,000 was paid for work done on tamoxifen at the University of

Kansas. Contracts such as these are routine in our industry. They are necessary to gain access to clinical research findings, data and analyses.

From the available records, Zeneca paid Dr. Bernard Fisher and Dr. Carol Redmond, about $11,000 over nearly twenty years to participate in educational programs and to appear before the FDA in support of our drug applications and filings. These activities are consistent with the accepted practices in our industry.

Over this same period of time, NSABP solicited funding from Zeneca and several other companies to help support NSABP meetings. According to available records, Zeneca's contributions towards these activities from 1976 through 1993 total approximately $585,000.

The purpose of the NSABP meetings was and is to bring NSABP cooperative researchers and others in the cancer research community together to share the latest information concerning cancer research. NSABP meetings were intense working sessions which covered topics related to the day to day problems and situations inherent in the running of, or the recruitment for, large clinical trials. NSABP controlled the agenda for their meetings and Zeneca had no influence over the scientific program. Continuing education credit was often available for attendance at these meetings.

Industry funding for dinners and receptions is a common and long accepted practice within this country's scientific community. Zeneca's conduct was entirely consistent with both the letter and spirit of FDA policy and the codes of conduct adopted by the American Medical Association (AMA) and the Pharmaceutical Research and Manufacturers Association (PhRMA), not to mention our own stringent internal corporate guidelines as they applied then and now.

Finally, in 1988 at the request of the University of Pittsburgh, Zeneca agreed to participate in the funding of a research chair at the University. The purpose of this chair was to assist the University of Pittsburgh's Department of Surgery in their stated desire to attract and recruit graduate students and faculty members interested in pursuing research in oncology in honor of Dr. Fisher. Zeneca has donated $600,000 to help establish the chair. It is our understanding that sufficient funds have yet to be raised to complete the $1.5 million endowment and the chair has not been created or filled.

We believe that our financial assistance to the University of Pittsburgh and NSABP contributed to breast cancer research in the U.S. and fostered a better understanding of breast cancer treatment around the world. We do not believe that this financial support caused NSABP to be less diligent in reporting safety information regarding tamoxifen. In fact, much of our financial support was given specifically to obtain extra safety reports to submit to the FDA and to facilitate the exchange of information among breast cancer researchers.

In conclusion, we at Zeneca are committed to the development and support of safe medicines backed by good science and proper scientific practices. We believe tamoxifen is a safe and effective medicine vital to the treatment of breast cancer. We deplore fraud and poor scientific practices in clinical research. We accordingly are pleased to assist the Subcommittee in this investigation.

My colleagues and I would be happy to answer any of your questions.

Mr. DINGELL. Thank you, Dr. Patterson.

Dr. Plourde.

Mr. PLOURDE. I do not have a prepared opening statement, Mr. Chairman.

Mr. DINGELL. We would be glad to recognize you for any comments you might like to make at this time.

Mr. PLOURDE. No, I think Dr. Patterson adequately reflected our comments.

Mr. DINGELL. Very well.

Mr. Milbauer.

Mr. MILBAUER. Mr. Chairman, I don't have a prepared statement, either. I am just here to help answer questions that the committee may have.

Mr. DINGELL. Very well, gentlemen. Thank you for your prepared statement.

The Chair recognizes the distinguished gentleman from Colorado for questions.

Mr. SCHAEFER. Thank you, Mr. Chairman.

Dr. Patterson, before we begin, I would like to give you an opportunity to allay the fears of some of the general public. Is tamoxifen effective in treating women with breast cancer?

Mr. PATTERSON. There is a very simple answer to that. Yes, sir, it is effective both in the advanced disease—and data on that has been generated over many years in many countries in the world—it is effective in treating the early disease as a so-called adjuvant therapy.

Those adjuvant therapy studies have been conducted also in many parts of the world. For instance, the NSABP data only represents approximately 10 percent of the major studies that have been conducted worldwide on adjuvant therapy of this stripe. Even if you were to remove all of the NSABP studies from the world overview of adjuvant therapy, the conclusions on efficacy and safety would remain the same.

Mr. SCHAEFER. How many studies have been conducted? Are we talking about a large number, small number? How many women have been involved?

Mr. PATTERSON. There are many hundreds of trials of this study throughout the world. In adjuvant therapy, for instance, there are approximately 40 major studies worldwide; but in the advanced disease and in other treatments, many hundreds.

Mr. SCHAEFER. Well, the news reports have been focusing not on the treatment trials but on the prevention trials; is that correct?

Mr. PATTERSON. That appears to be the case, sir.

Mr. SCHAEFER. That appears to be the case?

Mr. PATTERSON. The safety of tamoxifen for prevention has been the subject of much media discussion in this country.

Mr. SCHAEFER. I understand that—if I do understand it correctly, prevention trials involved giving tamoxifen to women with a high risk of getting breast cancer, but who, in fact, have not really contracted the disease; is this correct?

Mr. PATTERSON. That is correct. They simply do not have the disease.

Mr. SCHAEFER. You indicated in your opening statement that your company was asked to participate in prevention trials, but you

were reluctant to do so. I know that you covered this somewhat briefly in your opening statement, but I would like to give you an opportunity to expand on your answer.

Why was it that you were reluctant to participate in these prevention trials?

Mr. PATTERSON. When these were first mooted in 1985, we had concerns on a number of fronts, shared also by a number of scientists in the field. The drug had been developed as a medicine for cancer. Most of the studies had been in women with the advanced disease and had not been long term. It is not possible to do, for instance, placebo-controlled studies in advanced cancer, so the absolute profile of this agent was not absolutely clear; and whilst the animal toxicology was adequate for use as an anticancer agent, it certainly wasn't adequate for use in patients without cancer. So over the period 1985 to 1990, studies were done by the company.

Also, clinical studies were done, including studies by NSABP, where data on all of these subjects matured. By 1990, there were data on controlled studies on women treated for long periods of time with the drug, who had not got advanced disease, and therefore the side-effect profile could be recognized more clearly.

We had further animal toxicology which had included some very serious findings in the rat liver, which were a concern to us and to the outside world. And we also had a whole series, or a whole increased amount of safety information from large numbers of patients; and my company, in reviewing this situation, was concerned that although women at high risk of developing breast cancer clearly have a major worry as to whether they are going to develop the disease, and anything that one can do to help them has to be considered, that 50 percent of the women who develop breast cancer do not come from that group; and that even when a woman is at high risk of developing breast cancer, a relatively small number of those women will develop the cancer over a relatively short period of time.

And that meant that for the majority of the women taking part in such studies, all they could expect to get from a medicine such as tamoxifen was the side effects of this agent. It was unlikely to be protecting them, although there were some suggestions and there are some suggestions that it may prevent postmenopausal bone loss and it may also prevent cardiovascular diseases that result from the effects of cholesterol.

So it was a very difficult, risk-balanced equation; and that is clearly why it is being debated so hard in public.

Mr. SCHAEFER. But you were asked by the medical community, I think, to participate in these prevention trials; were you not?

Mr. PATTERSON. We were.

Mr. SCHAEFER. And you have given your answer. The NCI made this request as well, didn't they?

Mr. PATTERSON. NCI did make this request, made a request for the material for the trials.

Mr. SCHAEFER. Given your consent, you made it conditional, upon reviewing the consent form, that it was to be given to women to participate in the trial; is that correct?

Mr. PATTERSON. That is correct.

Mr. SCHAEFER. Some of these questions lead up to what I am going to be asking of witnesses in the future here. Did you, in fact, review the consent forms?

Mr. PATTERSON. We reviewed a model consent form in the fall of 1991, extensively within the company.

Mr. SCHAEFER. This was the form used in the trials, or was it changed without your knowledge and consent?

Mr. PATTERSON. The consent form appears to have evolved considerably over a period of time subsequent to this. This was the consent that was initially submitted, as I understand it, to the FDA by NSABP; and there were changes that occurred subsequent to that, which we did not review.

Mr. SCHAEFER. OK, so there were changes.

So you were basically unaware of the affirmative statement concerning uterine deaths that was at some point included in this consent form?

Mr. PATTERSON. We did not rereview the consent form and find that statement.

Mr. PLOURDE. Congressman, if I can add a statement to that——

Mr. SCHAEFER. Please.

Mr. PLOURDE. Although we were not aware that this change had been made early on, I believe we did become aware toward the middle of 1993 that this change had been made. However, at the time, we were told by the NSABP that indeed that was a correct and true statement.

Mr. SCHAEFER. Did you register any objection to this?

Mr. PLOURDE. We did not.

Mr. SCHAEFER. Was it a true statement?

Mr. PLOURDE. We were told it was a true statement at the time that we became aware that this was in the consent form, by the NSABP.

Mr. SCHAEFER. But is it a true statement, to your knowledge, at this point?

Mr. PLOURDE. No, it is not.

Mr. SCHAEFER. Let me turn to the issue of deaths arising from the trials.

You requested notification of any deaths; is that correct?

Mr. PATTERSON. That is correct.

Mr. SCHAEFER. You were notified of all the deaths?

Mr. PATTERSON. We were notified of all the deaths, yes.

Mr. SCHAEFER. Approximately how many death notifications do you routinely receive in the course of a year?

Mr. PATTERSON. Over the course of a year, over 100 patients are dying across the NSABP studies involving tamoxifen. We receive an annual printout or an annual computer diskette which contains data on large numbers of patients. The latest one contained more than 300 patients.

Mr. SCHAEFER. When the deaths are reported to you, is the cause of a particular death indicated?

Mr. PATTERSON. Deaths are reported to us in a number of different ways.

Again, perhaps just for clarification, women are expected to die in these studies. They are suffering from breast cancer. Death is not always an unexpected event, so deaths were reported to us as

routine or deaths were reported to us as a serious or unusual event or one that occurred on treatment; and there is a difference.

Mr. SCHAEFER. So was the cause reported to you?

Mr. PATTERSON. Causality was not linked to death, although—I am not trying to be difficult in answering your question. The way that the data were reported to us was that other factors associated with the death were listed in a separate column, but causality specifically was not reported.

Mr. SCHAEFER. Mr. Chairman, I see my light is on, and I will pass.

Mr. DINGELL. The time of the gentleman has expired.

The Chair recognizes now the gentleman from Ohio, Mr. Brown.

Mr. BROWN. Thank you, Mr. Chairman. I would like to follow up on some of Mr. Schaefer's questions about tamoxifen and some of the—both the prevention—particularly the prevention trials.

Dr. Patterson, based on what you said, I would infer that it is very important for Zeneca to be kept informed in a timely way of information regarding side effects being generated in Dr. Fisher's breast cancer treatment trials, correct?

Mr. PATTERSON. That is correct.

Mr. BROWN. How and when did your company convey to Dr. Fisher, other officials in NSABP, the importance of timely and accurate information regarding any side effects of tamoxifen?

Mr. PATTERSON. Over the course of the more than 14 years in which we were associated with studies that they were conducting, my company on many occasions interacted with Dr. Fisher and NSABP on the issue of side effects. We discussed these about them, we wrote memos to them, we had an agreement with them, the most recent of which was in 1986, on exactly what side effects data would be reported to us and when.

Mr. BROWN. One of the key side effects that Zeneca was concerned about was endometrial cancers, correct?

Mr. PATTERSON. Correct.

Mr. BROWN. When were you first notified that at least one uterine cancer death had occurred with the cause attributed to tamoxifen?

Mr. PLOURDE. Mr. Congressman, maybe I can try to answer that.

As part of our annual obligation to report adverse events to the FDA, we requested a number of items from the NSABP; and on a yearly basis we got the following information:

We asked them to provide us with a listing of deaths or withdrawals occurring while on treatment in those various trials that we held. In addition, we asked for a computer diskette on second tumors, and those tumors are malignancies that occur after the diagnosis of breast cancer. In addition, we also take information obtained from the NSABP annual report to its membership, which contains adverse effects, contains narratives on serious adverse reactions, and it contains information on overall survival.

In February of 1992, we received information on a death in a patient who had the diagnosis of endometrial cancer. We requested further information from the NSABP in regards to this patient, and I reviewed that information and assessed the death to be attributable to endometrial cancer. However, one must keep in mind that

the cause of death is often very difficult to establish and involves some medical judgment.

I did have a discussion with the NSABP in regards to this death, and it was their belief that this patient had died from other causes, other than endometrial cancer. Hence, I reported to the FDA the information that I received, which included the possible relationship to endometrial cancer as well as to pulmonary embolus.

As Dr. Patterson mentioned in his opening statement, most recently we were informed that we allegedly had information on a second endometrial cancer death in February of 1993, and that was included in the computer diskette. The diskette information not only includes the second tumor data that occurred in that particular trial, but also the survival status of the patient at the time of the report. There is no causality mentioned in that particular report, and it was not possible at that time, neither is it possible now that—in reviewing that data to really make an association between endometrial cancer and the death of this particular patient.

We were dependent on the NSABP to medically review this information and to provide us with this data, so the first time, given the scenario that I have just stated, that Zeneca appreciated the deaths had occurred related to endometrial cancer was actually in December of 1994.

Mr. BROWN. So you are saying that the December 1993 case was where you were notified by NSABP that tamoxifen was the cause of the uterine cancer specifically, precisely?

Mr. PLOURDE. No, I think in December of 1993 we were informed that the patient's death had been attributable to the endometrial cancer in a patient taking tamoxifen.

Mr. BROWN. How were you informed of that?

Mr. PLOURDE. I was called by a member of the NCI and informed that there had been a death reported at the NSABP meeting.

Mr. BROWN. NSABP did not call you? NSABP said it at a meeting, Dr. Fisher said it at a meeting, NCI then called you? You have not to this day heard it directly from NSABP?

Mr. PATTERSON. We subsequently have had information from NSABP, in December, listing the patients who have died and giving the identifiers.

Mr. BROWN. What triggered that? You called NSABP, they acknowledged that was the case, but NSABP never initiated the call to you about that death or subsequent deaths?

Mr. PLOURDE. That is correct.

Mr. BROWN. Is that the way NSABP should be operated?

Mr. PLOURDE. No. They should be providing that information to us as soon as it is known to them.

Mr. BROWN. Why didn't they call you? What is your view of why they didn't call you?

Mr. PLOURDE. It is difficult to speculate. I suspect that their priorities in regards to informing us were different than ours, but I really couldn't say why they didn't call.

Mr. BROWN. It is not like they didn't notify somebody they didn't know. You had this long-term, dozen-plus years relationship with them; they know you, you know them; you would over time emphasize the importance of that two-way exchange of information; they

simply failed to notify a very important colleague, if you will, of theirs?

Mr. PATTERSON. It is conceivable that they didn't recognize these as endometrial cancer deaths until December 1993, but you would have to ask NSABP.

Mr. BROWN. Once Zeneca learned of these deaths, what were your responsibilities and whom did you inform as your duty to the public? What was the next step once you found this sort of indirectly through NCI?

Mr. PATTERSON. Our step is to inform the FDA in a timely fashion, and as necessary, or if necessary, to alter our package insert with the statement then that is read by all doctors using the drug.

Mr. BROWN. Did the information about the deaths necessitate any changes in the consent form for either the prevention studies or the treatment studies?

Mr. PATTERSON. The consent form for the prevention studies has been changed to remove the statement that there have been no deaths.

Mr. DINGELL. The time of the gentleman has expired.

The gentlewoman from Pennsylvania.

Ms. MARGOLIES-MEZVINSKY. Clarify something for me. From what we understand, the NSABP presented the information in October at a conference. Tell me where the time lapse is.

Mr. PLOURDE. There was an annual NSABP meeting in October of 1993 where the endometrial cancer data was presented. I was in attendance of that meeting. However, a lot of information was being conveyed; there were two projectors going on simultaneously.

And I was taking copious notes, and I did not note at that particular time that this particular death had apparently been mentioned in the presentation; and this was duly noted by a member of the NCI.

Ms. MARGOLIES-MEZVINSKY. So in other words, what happened was that, at some point, the information had not been thoroughly gone through, and it fell through the cracks?

Mr. PATTERSON. Can I answer that, Congresswoman?

It would be very unusual for any group to report a death to us or to any other person by means of standing up in a public meeting or trial—a meeting such as that one.

Furthermore, unless that patient's trial number were given, we couldn't identify that patient and deal with it appropriately, so we would expect to be notified in writing or by a telephone call directly, not to just happen to be sitting in a meeting where something like that is presented.

Ms. MARGOLIES-MEZVINSKY. Do you know why you were not notified?

Mr. PATTERSON. No, I don't.

Ms. MARGOLIES-MEZVINSKY. Dr. Patterson, once Zeneca had learned of these deaths, what was your responsibility and whom did you inform—did you turn to with regard to these deaths?

Mr. PATTERSON. The first responsibility, as a pharmaceutical company, is to notify the Food and Drug Administration; and we did that in early January of 1994.

The second responsibility is to inform doctors or patients associated with use of the drug of that occurrence if it is germane to

their treatment. In patients who are treated with tamoxifen for breast cancer, we had recognized since 1989 that endometrial cancer, uterine cancer was occurring; and it is recognized that 15 to 20 percent of women who develop endometrial cancer will die of that disease, as I said in my opening statement, so some deaths were not unexpected.

The issue really relates here to how use of the drug for breast cancer can be translated across into a prevention situation where the odds of death are significantly different.

Ms. MARGOLIES-MEZVINSKY. What about labeling? Did it have any effect on labeling?

Mr. PATTERSON. The labeling was changed in April of this year to include the statement—on the fact that there has been a death.

Ms. MARGOLIES-MEZVINSKY. Did the information about the deaths necessitate any changes to the consent forms for either the prevention or the treatment studies?

Mr. PATTERSON. It clearly had an effect on the prevention consent form, and I believe that has been changed. In the studies of more advanced breast cancer, statements have been in the consent for a number of years stating that uterine cancer was a potential risk of taking tamoxifen; and it has usually been included in the potentially fatal toxicity section of the protocol.

I don't believe there were any statements in most of those consent forms—although Dr. Plourde may want to add to this—about the fact that there had been no deaths, and some deaths would regrettably be expected.

Ms. MARGOLIES-MEZVINSKY. In determining the then existing consent form needed to be changed, were you surprised at all to learn that the contents of the consent form were what they were?

Mr. PATTERSON. Yes.

Ms. MARGOLIES-MEZVINSKY. Could you elaborate, please?

Mr. PATTERSON. Although we had reviewed a consent form in the fall of 1991, that had not contained a statement that there had been no deaths. That statement had been introduced subsequently, and we had not reviewed subsequent consents. Those consents had been sent to the company, but with covering letters detailing the changes to both protocol and consent; and there was no—our attention was not drawn to that fact, so it was not—it was a surprise to us that there was a problem in this area.

Ms. MARGOLIES-MEZVINSKY. Do you know who added the statement?

Mr. PATTERSON. I do not know.

Ms. MARGOLIES-MEZVINSKY. What about the existing consent form for the prevention study, what about it stood out to you?

Mr. PATTERSON. I don't think I understand your question.

Ms. MARGOLIES-MEZVINSKY. What about the existing consent form for the prevention study stood out?

Mr. PATTERSON. The one that exists today?

Ms. MARGOLIES-MEZVINSKY. Yes.

No, the one that existed then.

Mr. PATTERSON. At the time, when the company reviewed it, the company felt that from its knowledge of the toxicity of tamoxifen, it was quite a good consent form; but there were a number of things that were in our package insert that were not fully covered

in that consent, and Dr. Plourde wrote to NSABP informing of that at the time that we reviewed it.

Ms. MARGOLIES-MEZVINSKY. The consent form used at that time had a statement in it that no endometrial cancer deaths had been reported due to the use of tamoxifen, correct?

Mr. PATTERSON. At the time the study was initiated in June 1992, my understanding is, yes, that statement was in there.

Ms. MARGOLIES-MEZVINSKY. Was that statement in the original version of the consent form for the prevention study?

Mr. PATTERSON. I am sorry, I didn't hear you.

Ms. MARGOLIES-MEZVINSKY. Was that statement in the original version of the consent form for the prevention study?

Mr. PATTERSON. The one that we reviewed, it was not in it.

Ms. MARGOLIES-MEZVINSKY. Thank you very much.

Mr. DINGELL. The time of the gentlewoman has expired.

The Chair now recognizes the gentleman from California, Mr. Moorhead.

Mr. MOORHEAD. Thank you, Mr. Chairman.

Did approximately the same number of women take the placebo that did the tamoxifen?

Mr. PATTERSON. Which study are you referring to, Congressman?

Mr. MOORHEAD. The study that you have been referring to.

Mr. PATTERSON. The Study B-14?

Mr. MOORHEAD. Yes.

Mr. PATTERSON. Yes, that is correct.

Mr. MOORHEAD. Have any of the women who took the placebo come down with uterine cancer?

Mr. PATTERSON. There have not been any deaths from uterine cancer in those patients, to our knowledge.

Mr. MOORHEAD. What percent of the women that took the tamoxifen have come down with uterine cancer? How many have taken it and how many came down with the illness?

Mr. PATTERSON. It is about 25 out of 1,400 are the numbers that come to my mind, but I don't have those numbers in my head, Congressman.

Mr. MOORHEAD. Twenty-five out of 1,400. Of those women that took the placebo, how many eventually got breast cancer? They were people——

Mr. PATTERSON. Had a recurrence of their disease?

Mr. MOORHEAD. Yes.

Mr. PATTERSON. Again, sir, I don't have those numbers.

Mr. PLOURDE. Congressman, maybe I can provide some information on that.

Two patients in the B-14 trial——

Mr. PATTERSON. Did you ask of breast cancer or——

Mr. MOORHEAD. What I am trying to see are the benefits versus the risks; and if the tamoxifen patients were saved from cancer, from breast cancer in substantial numbers, I want to see whether the risk was worthwhile. Do you see the direction I am going?

Mr. PATTERSON. Yes, I do, indeed.

Mr. PLOURDE. Unfortunately, all of the adjuvant breast cancer studies, when they were initiated, were not designed to provide us with information on endometrial cancer. When this was determined in follow-up, this was investigated quite carefully. Unfortunately,

due to the various biases of the trial, because they weren't set up in proper form, it is difficult to assess as to the incidence of breast cancer in a placebo group. In fact, the two patients that were randomized to placebo in the B-14 trial did receive tamoxifen subsequently and had breast cancer.

Mr. PATTERSON. Can I try and answer your question for you?

There are less women who developed recurrent breast cancer in the placebo group than in the treatment group. The absolute numbers, I don't know off my head, but about ⅓ less developed recurrent breast cancer in the treatment group than in the placebo group. That approximated—if you look then at deaths, where there was a 20 percent reduction compared with the—for the tamoxifen group compared to the placebo, there have been 4 deaths from endometrial cancer. We are talking about a 20-fold difference between those two groups, so we are talking about, I think, 80 deaths versus 4 deaths.

Mr. MOORHEAD. I would think those figures in that information would be something that was very important to give to women that might be considering using the drugs so that they could weigh the risks one way or the other.

Mr. PATTERSON. I would agree with you.

Mr. MOORHEAD. Dr. Patterson, on several occasions, Dr. Fisher requested funding from Zeneca. Did he ever ask for funding for improving his administrative staff?

Mr. PATTERSON. Not to my knowledge.

Mr. MOORHEAD. But did he ask for funding for receptions at the NSABP meetings?

Mr. PATTERSON. Yes, he did.

Mr. MOORHEAD. Did he get that?

Mr. PATTERSON. Yes, he did.

Mr. MOORHEAD. If he had asked for funding for administrative staff, do you think he would have gotten it from you?

Mr. PATTERSON. It is in our interests and everybody's interests to ensure that the data from these studies are as good as they can be; and I am sure we would have responded positively to that kind of request.

Mr. MOORHEAD. You have had a total of 25 deaths now from uterine cancer?

Mr. PATTERSON. A total of 25 patients have developed uterine cancer. There are only four deaths.

Mr. MOORHEAD. I see. Can you tell whether it came from the—how many of these women would have gotten uterine cancer whether they had taken tamoxifen or not?

Mr. PATTERSON. That is a difficult question. The incidence of uterine cancer as a background in the population is one way that you can look at that, but the control group is the other; and there are actually no uterine cancers in the control group which, in itself, is surprising. You would have expected in that number of women of that age group over that period of time to have had some of those occur, but that has not been the case.

Mr. MOORHEAD. That is why I was interested in knowing how many of those who had taken the placebo had eventually come down with the uterine cancer. I think that would be something that

would help you understand the pluses and minuses of taking the drug.

Mr. PATTERSON. We have calculated from our worldwide databases how the incidence of endometrial cancer on patients taking tamoxifen varies from the background incidence in the population at large. Patients with breast cancer do have an increased incidence of uterine cancer anyway, but it looks to us as if the increase associated with tamoxifen is somewhere between two- and fivefold over the background incidence, taking all of the studies we are aware of worldwide together.

Mr. MOORHEAD. I guess the last question—and you probably can't answer it—but because of the benefits of tamoxifen, obviously not liking the dangers that come to the few who take it, is it possible to find any other drug or any change in tamoxifen that might eliminate that risk?

Mr. PATTERSON. Yes, it is possible to try and find an antiestrogen that would be called a pure antiestrogen, that is, it had no effects on the uterus of the kind that we are describing; and that has been the subject of research in my company and a number of others for many years. It is possible that such agents will be developed or even that a partial agonist antiestrogen, of which tamoxifen is one, that didn't have those particular positive effects on the uterus might also be possible to be developed; and there may even be one or two in very early-stage research at the moment.

Mr. MOORHEAD. You are dealing with a subject that is of great concern to every husband in the world, I am sure, because of wanting to protect their wives, and when things like this come up you wonder why it gets members of the committee excited. It is because they are concerned for their loved ones.

mr. PATTERSON. It touches us all, Congressman.

Mr. MOORHEAD. Thank you, Mr. Chairman.

Mr. BROWN [presiding]. Thank you, Mr. Moorhead.

Dr. Patterson, returning to the 1993 time period that both I and Mr. Schaefer earlier had asked about, the subcommittee obtained records out of NSABP depicting a slide presentation dated in August of 1993, not just the October, and we talked about the October seminar, but a slide presentation August, 1993. And that slide presentation there are at least two deaths attributable to—two deaths that were attributed from that cancer, from endometrial cancer, in the B-14 study with patients taking tamoxifen.

It should be in front of you. One is numbered 006252, where a patient died, and the other one was number 006254. Were you aware of this information in August, 1993?

Mr. PATTERSON. I am not aware that any member of the company received that slide presentation or that we were informed of it by the NSABP.

Mr. BROWN. Why did it take 4 months? We know that was prepared in August. We are not saying that you knew about it in August. We know it was prepared in August. Why did it take that—take 4 months from the time these slides were prepared to inform you, as the manufacturer, of these deaths?

Mr. PATTERSON. That is a question you must ask NSABP. I don't know how to answer that.

Mr. BROWN. Isn't it true that by the summer of 1993, when the information was being prepared for these slides, if they were actually prepared by August that if the information was being prepared in the summer that Zeneca was pressing NSABP regarding any incidence of endometrial cancers associated with tamoxifen? Were you doing that?

Mr. PATTERSON. Yes. We had been conducting worldwide review of this particular subject. We had pressed NSABP very hard for their up-to-date information, and we were convening a panel of experts to help us to review the situation on endometrial cancer.

Mr. BROWN. So you don't know why this information, then, wasn't provided to you as you were holding these conversations with them?

Mr. PATTERSON. No, we don't nor why it wasn't recognized in their consent form for prevention.

Mr. BROWN. In your testimony you indicated that Zeneca had provided upwards of a million and a half dollars in direct support to the University of Pittsburgh to NSABP for a variety of projects. Was that money solicited or unsolicited? Did Zeneca volunteer it or did Pittsburgh and NSABP request it?

Mr. PATTERSON. The money, which was paid over a period of some 20 years, divides into several different categories, some of which were requested, some of which were volunteered.

For moneys for data handling and analyses that we required of them to allow us to put our FDA applications in, that was money that we offered to them in return for the work that they had to do over and above their normal study work to achieve those analyses.

Mr. BROWN. So did you feel obliged to provide them those funds in some manner?

Mr. PATTERSON. That would be absolutely normal practice for us to do that, yes.

Mr. BROWN. What kind of benefits did you enjoy by providing these funds?

Mr. PATTERSON. The funds for the data handling allowed us to provide information to the FDA on the beneficial effects of tamoxifen in Studies B-9 and B-14 in particular, and also to provide, as far as we could, a risk-benefit analysis by providing side effects and adverse reaction information on those studies and on all other tamoxifen studies conducted by NSABP.

Mr. BROWN. Did you know that some of that money, to the tune of hundreds of thousands of dollars, were going to some of the parties and other entertainment that Chairman Dingell mentioned?

Mr. PATTERSON. That was by separate request, so the data for—the data handling was separately requested for the data——

Mr. BROWN. Separately requested by Dr. Fisher or by whom?

Mr. PATTERSON. By the NSABP, yes. They didn't request the money for the data handling. We requested the information for which we offered money for them to provide us with that scientific information. The money for the receptions at the NSABP annual meetings or biannual meetings was requested of us by NSABP for that specific purpose.

Mr. BROWN. You say receptions. Chairman Dingell made it look a little more elaborate than receptions. But you knew that money was to be used for that purpose?

Mr. MILBAUER. Yes, Congressman. If I could answer that, as you know or as perhaps you don't know, NSABP would hold biannual and then it became annual meetings for the purpose of bringing together all of their cooperative researchers to be able to discuss over a period of 3 or 4 days how trials ought to be run, what new protocols ought to be considered, discuss the analyses of information that would go on. And these were heavy scientific sessions that would take place over these 3 or 4 days.

On one evening they would hold—they would want to hold a social event. And we were asked, and it began almost 18 years ago, if we would sponsor such an event. These were receptions. These were receptions that were not sit-down dinners. They did provide food, hors d'oeuvres, if you will, and cocktails, but these were—this was an integral component of the opportunity for these researchers to get together in an informal session, exchange information.

We didn't control and had no involvement with the agenda for such meetings, and these are all within the guidelines that are published by the American Medical Association with respect to making sure that the substantial majority of the time devoted to these scientific meetings were devoted to the sessions and that the expenses were modest and that they did facilitate exchange. And within the spirit of that, that is what we were sponsoring over these many years.

Mr. BROWN. Modest. Two things come to mind when you say they were modest, and you continue to use the word reception. I have not been to a lot of receptions that cost in the rough ballpark of $50,000 to $80,000, which several of these cost. And, second, these weren't held in Pittsburgh. They were held in Hilton Head. They were held in the Canadian Rockies.

I am not disputing your right as a private corporation to do that. I am just questioning your labeling of some of these as educational, as routine, as simple receptions.

Mr. MILBAUER. Well, Congressman, let me address that for you. It is common practice between the pharmaceutical industry and scientific institutions and medical institutions to sponsor and help in the conduct of those meetings, but I think it is important to distinguish. We did not choose the venue for the meetings. The venue, whether it was in Bal Harbour or in San Francisco, that was chosen by the NSABP. We had no role——

Mr. BROWN. But they also knew they had a sugar daddy to help them defray the expenses.

Mr. MILBAUER. The only expenses we believe to our knowledge that was defrayed in terms of administrative expenses, because it is a nonprofit organization, was the reception that evening. Our funds, to the best of our knowledge, were not utilized in the accommodations for the attendees nor for the transportation to those meetings.

And, in fact, I think it also was important when you look at a $50,000 or an $80,000 reception is that the numbers of attendees at these meetings grew over the years. That is, there were only about 6 or so receptions of some almost 30 that were in that, but the number of attendees approached 1,000 or even more than that on some occasions.

Mr. BROWN. I would yield to you, Mr. Schaefer.

Mr. SCHAEFER. Two quick questions. Were any Federal moneys involved in the sponsoring of these receptions?

Mr. MILBAUER. To the best of my knowledge, there were no Federal moneys provided for the reception. In fact——

Mr. SCHAEFER. How about transportation, lodging, et cetera?

Mr. MILBAUER. I don't know. It would be whatever NSABP would fund. They may have gotten that from NCI, but we were actually advised by the NSABP that they could not get funding from the Federal Government for the reception. And it was on that basis—they would ask other companies to help sponsor the meetings, and this was the way——

Mr. SCHAEFER. I am talking about the reception alone. I mean the transportation down, the lodging, everything else.

Mr. MILBAUER. To the best of my knowledge, there was no Federal funding for the reception.

Mr. SCHAEFER. For the reception only. All right. And you paid 100 percent of the reception?

Mr. MILBAUER. Yes. We would pay those to the hotel or we would pay those to a meeting planner. We did not pay those moneys to the NSABP or anyone else. It was just for those arrangements.

Mr. SCHAEFER. All right. Well, we will ask questions about transportation and lodging later.

Mr. BROWN. I would add that the transportation to these places other than Pittsburgh was apparently borne by the Federal Government.

One further question about this, and then I have a brief set of questions. You recently dropped your contribution to NSABP from the $50, $60, $70, $80,000 range down to $10,000. Yet you make these statements that they were routine, and they were simply reception. Why did you drop that amount?

Mr. MILBAUER. I believe that the meeting of $10,000 was a second meeting in 1993, and I think it was just—I don't recall whether the request was for—in fact, I don't know what reception took place at that meeting, but we just funded it to $10,000.

The prior time we actually just provided them with a grant because during that time it was unclear as to whether the kinds of sponsorship of these meetings would be within the guidelines because the guidelines were evolving.

Mr. BROWN. So, number one, what was the amount of the grant? Second, are you going back up to the $50,000 to $80,000? Is the $10,000 just a temporary drop just prior to this hearing and then back to the 50,000, 80,000?

Mr. MILBAUER. The $10,000 was provided in 1993.

There is actually a meeting that is taking place at the present time. We were requested to provide the typical sponsorship.

We received a request earlier this year. At the time, we deferred responding to that, and I think, despite the fact that we think there is no impropriety at all, in fact we have reviewed the guidelines. We keep looking at them to determine that they are within the guidelines. We believe they are, but given the publicity and given the fact that there was going to be this hearing today, we had declined in providing support to this meeting, and in fact NSABP's response to that is, given the situation, they would not want to put themselves into a position of receiving moneys for that.

But I would say affirmatively on the basis of what the guidelines and how they operate, we see nothing wrong with what we have done in the past.

Mr. BROWN. To change the subject, is your parent company ICI? Is there still affiliation with ICI?

Mr. PATTERSON. No, we are now a separate company. Zeneca is a totally separate share holding company.

Mr. BROWN. When was ICI—when was the disaffiliation, if you will?

Mr. PATTERSON. In 1991. I am sorry, 1993. My apologies.

Mr. BROWN. ICI is to my understanding, if you can help me with this, the manufacturer of DDT and a distributor of DDT?

Mr. PATTERSON. I don't think that I can answer for what ICI does. I am not an employee of ICI. I am a physician working in a pharmaceutical company.

Mr. BROWN. I understand that. I am only asking if, in fact, that is the case. If these companies were affiliated, I would think that you would know whether or not ICI manufactured DDT.

Mr. MILBAUER. It would be a speculation on our part, but I believe that they do not manufacture DDT, but I can't say with any certainty whether ever in its history that they have.

Mr. BROWN. OK. I was just curious because the information that I have been given is that ICI does, in fact, manufacture DDT and that I find it curious that companies that are affiliated—one is doing such good research on breast cancer as you have done, and if you are not—if you have no knowledge of whether it manufactures DDT and whether DDT—if there is any scientific proof of whether DDT actually increases the risk of breast cancer, we will drop it at that.

Mr. MILBAUER. I think probably the best thing—and I would agree with Dr. Patterson—is for the committee to receive some information from ICI with respect to whether they do or they don't.

Mr. BROWN. Other questions?

Thank you, gentlemen——

I am sorry, Mr. Schaefer, the gentleman from Colorado.

Mr. SCHAEFER. Two quick questions. Then I want to jump back to this 1992 death. After you made the determination that the death resulted from uterine cancer, you did notify the FDA; is that correct?

Mr. PLOURDE. That is correct.

Mr. SCHAEFER. Did you notify Dr. Fisher?

Mr. PLOURDE. I don't recall if I spoke to Dr. Fisher or to his assistant, Dr. Wickerham.

We do know—and we have records that we obtained further information in this case from Dr. Wickerham. Upon review of that information I did discuss the case with Dr. Wickerham, who felt that this patient had actually died of a pulmonary embolus rather than endometrial cancer.

However, given the problems in accurately interpreting the cause of death, I reported to the FDA that it was possible that this woman had died from endometrial cancer, contributed by pulmonary embolus.

Mr. SCHAEFER. Let me get this straight. You said that you don't recall whether or not you notified Dr. Fisher.

Mr. PLOURDE. The NSABP was notified, but Dr. Fisher himself, I can't say for certain that I notified him personally of that.

Mr. SCHAEFER. You can't remember that?

Mr. PLOURDE. I can't recall. I know I have had discussions with the NSABP, Dr. Wickerham, in this matter.

Mr. SCHAEFER. Should the NSABP have been able to determine the cause of this patient's death?

Mr. PATTERSON. The NSABP had access to the full case record forms, access to the hospital where the patient died and was treated. We only had access to a one-paragraph summary.

Mr. SCHAEFER. I understand that. I am asking a question, though. The NSABP—could they have determined the cause of the death?

Mr. PATTERSON. They can determine the cause of death. They could have as per their judgment, but cause of death is not an easy judgment medically.

Mr. SCHAEFER. Should they have done this?

Mr. PATTERSON. With a retrospectroscope, they clearly have determined that to be the cause of death, but at the time they did not.

Mr. SCHAEFER. They did not. Thank you.

Mr. BROWN. Thank you, Mr. Schaefer.

Gentlemen, thank you for your testimony. Appreciate your being here.

The Chair will now call up the second panel: Dr. J. Dennis O'Connor, chancellor, University of Pittsburgh; Dr. Ronald Herberman, interim chairman, National Surgical Adjuvant Breast and Bowel Project; and Dr. Thomas Detre, senior vice chancellor for health sciences.

Dr. O'Connor, Dr. Detre, Dr. Herberman, welcome. In front of you are the rules of the subcommittee, the committee, the full committee, and the House of Representatives. Feel free to consult these throughout.

You are allowed certainly to have legal counsel here, and it is the tradition of this committee to testify under oath, if you would raise your right hand.

[Witnesses sworn.]

Mr. BROWN. Please be seated.

Dr. O'Connor, would you begin with your opening testimony, please?

TESTIMONY OF J. DENNIS O'CONNOR, CHANCELLOR, UNIVERSITY OF PITTSBURGH, ACCOMPANIED BY THOMAS DETRE, SENIOR VICE CHANCELLOR OF HEALTH SCIENCES, AND RONALD B. HERBERMAN, INTERIM CHAIRMAN, NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT

Mr. O'CONNOR. Thank you, sir.

Mr. Chairman and members of the subcommittee, I am Dennis O'Connor, chancellor of the University of Pittsburgh, and I sincerely thank you for accommodating my request to appear here today. I asked to come because I want to state in person that, as the senior executive officer of the University of Pittsburgh, I accept responsibility for the past administrative deficiencies of the National Surgical Adjuvant Breast and Bowel Project, which is

headquartered at our university. I also accept and welcome the responsibility to make things right.

I have stated these commitments to Dr. Broder, the Director of the National Cancer Institute, as well.

I deeply regret and apologize for any anxiety induced in cancer patients and the general public as a result of this matter. I am particularly sensitive to this unfortunate outcome because my wife is an oncology nurse who specializes in helping women with breast cancer to cope with the stress of their condition.

As my colleagues, Drs. Detre and Herberman, will describe to you, a large team consisting of many of the University's most able people, as well as outside experts, have been working diligently to make the changes that we believe are warranted to justify restored public confidence in us and to advance this important and historic research.

Mr. Chairman, as you know, there has been no shortage of public comment on this matter, with several hundred news accounts published and broadcast already. The media commentary is, on balance, healthy, for it heightens public awareness of the issues and the awareness of the University faculty and administrators. But I do want to identify two points that some of the news accounts may have obscured rather than clarified.

While it is gratifying and reassuring that, as far as is known, NSABP's research findings continue to be entirely sound, charges of deficient administration are not adequately answered by merely asserting that the research findings remain valid. Falsified data is odious under any condition.

Second, while credit for the intellectual achievements of a faculty member goes to that faculty member, the university is ultimately responsible for the administration of research. All honor that is due Dr. Bernard Fisher and his colleagues for their achievement in this path-breaking breast cancer research is their honor. We fully recognize, however, that the responsibility for competent research administration ultimately rests with us at the University.

To learn and to teach from observation and experience is the central mission of a University and the essence of science. What are some of the lessons we can learn from this experience? What can we now teach based on this experience? These large and difficult questions are being considered intensively. I am not yet ready to offer a complete list of possible answers, but I am ready to suggest several.

First, we must establish better mechanisms to ensure that even our most experienced, tested and accomplished faculty are responsive to administrative imperatives as well as to their pressing and sometimes compelling intellectual agendas.

We must find better ways to promote an environment in which faculty understand that the University's proper oversight in areas of administrative compliance neither conflicts with academic freedom nor collides with institutional respect for faculty members' judgment.

Those of us who have an administrative role in the universities must constantly remind ourselves that while loyalty to colleagues is important, depending on the facts of the case, accountability to the public supersedes that relationship.

We must be very sensitive to the importance of accurately disclosing in a timely manner emerging research developments that carry potential to affect the public adversely, even where there may be some uncertainty as to the facts.

We must elicit from research sponsors clear statements of their needs and expectations. When we receive such statements from research sponsors, we must follow the statements punctiliously. If we disagree with the statements, we must take the initiative to achieve a meeting of the minds. If the statements are unclear, we must get them clarified. Ambiguity in matters of administrative responsibility can undermine relations with research sponsors and indeed disserve the public.

The role of this subcommittee and its staff in this matter requires special note, and I will speak candidly. Mr. Chairman, as you yourself have stated, this subcommittee has a reputation for sharp teeth. Few relish being investigated by this subcommittee. During the last 2 months we have had a fairly grueling set of interactions, document productions, interviews and information demands from the subcommittee staff. This work has been painstaking and not particularly pleasurable.

However, I also wish to acknowledge that the subcommittee and its staff, once the facts were collected, dissected and analyzed, did not shrink from working very constructively with the National Cancer Institute and the University to get the NSABP research back on track, to preserve the best of NSABP, and hopefully enable us to improve the rest.

If, in the end, the approach taken by this subcommittee had been negative and destructive rather than positive and constructive, breast cancer patients, present and future, would have been subjected to further suffering. Instead, they are being helped because of the advancement of a healthier partnership between NSABP and NCI that prevailed before. This subcommittee has been instrumental in that.

We are learning that sharp teeth can be painful and embarrassing but, unfortunately, can also be necessary from time to time.

We will not claim today, Mr. Chairman, to know with mathematical precision exactly the right mix of breathing room and oversight that is required at a University to produce great science, to generate medical knowledge, to save lives and alleviate suffering. Toward that ideal balance we strive imperfectly. Be assured, however, that the knowledge that we are and will always be imperfect does not discourage us. This episode motivates us to work harder to achieve these goals, which we share with the Federal Government and the American people.

Thank you, sir.

Mr. DINGELL. Thank you, Dr. O'Connor.

Dr. Detre.

TESTIMONY OF THOMAS DETRE

Mr. DETRE. Mr. Chairman and members of the subcommittee, I am Dr. Thomas Detre, senior vice chancellor for Health Sciences.

Mr. DINGELL. Doctor, the Chair apologizes. We have a miserable public address system, as you will find.

Mr. DETRE. My apologies. Can you hear me now, Mr. Chairman?

I am here in response to your invitation to comment on the NSABP matter and to answer your questions.

Mr. Chairman, after even more than 40 years in America, I still speak with an accent. When I came to the United States several years after World War II, physicians like myself who had accents were desperately needed because of the shortage of skilled scientists in America's University hospitals and laboratories. But now I am happy to report people like me are rather obsolete because today there are so many exceptionally able American scientists. Today, most of the time, American senior faculty train foreign students, as well as American students, not vice versa. That is the amazing progress of American science in our lifetimes.

During the same period, as you know, along with spectacular advances in biomedical research in the United States, the science of treatment evaluation also progressed rapidly. The multi-center clinical trial, of which NSABP is a renowned example, is universally regarded as a premier approach for testing medical hypotheses.

Dr. Bernard Fisher has spent his lifetime developing such trials to gauge the efficacy of breast cancer treatments. These trials notably involved his historic discovery that lumpectomy followed by radiation is fully as effective as the more devastating and disfiguring radical mastectomy which, before Dr. Fisher's discovery, was the treatment of choice for many forms of breast cancer.

This landmark finding, I might add, has since been confirmed independently by at least five large-scale clinical trials in the United States and Europe.

One of the advantages of a multi-center clinical trial over the usual study conducted in a single or several academic medical centers is that the multi-center trial can test a very large number of patients in diverse geographical, socioeconomical and medical settings, making the results more readily subject to generalizations about the population at large. Biostatisticians also note the tendency of such large studies to be valid by reason of the studies' statistical power.

A drawback of the broad scale multi-center clinical trial, however, is the difficulty in controlling the quality and uniformity of the data coming from numerous investigators in numerous centers, some of whom are not highly expert in conducting such research. This difficulty may explain some of the current issues relating to NSABP. I say explain, I do not say excuse.

We still do not know nor does the National Cancer Institute, with complete and total thoroughness, exactly what fraction of the NSABP data were unreliable. We are still double checking, as is NCI. But based on everything we know to date—and it is extensive—and despite the wide-ranging questions about certain NSABP administrative practices, that no knowledgeable person has challenged the continuing validity of the scientific conclusions.

I report this conclusion to the subcommittee not to minimize concerns about our responsibility to administer by the highest standards but to reassure breast cancer patients and their families, as have the responsible government agencies, that public health and safety are not compromised. The soundness of the scientific conclusions is not the issue before us today.

However, in retrospect, I believe that the academic community has failed to arm patients, their families and the advocacy groups with sufficient information about clinical trials to protect them from the overwhelming anxiety that they experienced when they were confronted with the news that some data in these trials were flawed. I am sure that in collaboration with NIH we can do better.

We are here because, notwithstanding the soundness of the scientific conclusions, the quality of administration of NSABP has been questioned. In close coordination with the National Cancer Institute and other cognate agencies, we at the University have been working very, very intensively to identify, analyze and respond to each of these concerns.

For example: The University appointed one of its most distinguished senior scientists, Dr. Ronald Herberman, to be interim head of NSABP pending the ongoing reviews and reforms. Dr. Herberman, who served as an NIH scientist for many years before coming to the University of Pittsburgh, agreed to take on this heavy and thankless burden, making only the request, which we will honor, that as soon as a permanent NSABP chair is in place he will return to his duties as head of the Pittsburgh Cancer Institute.

We are committed to finding the best possible candidate to be permanent NSABP chair and are now conducting a national search for a nationally recognized and distinguished surgical oncologist to serve in that role.

We have proposed and are committed to the implementation of a new permanent NSABP leadership structure to ensure that the project will be run in a manner that justifies high public confidence.

NSABP, under the interim leadership of Dr. Herberman and his colleagues, proposed, and the National Cancer Institute accepted—after many extensive and substantive interactions—a comprehensive NSABP plan for corrective actions. Dr. Herberman will describe the highlights of that plan to you. I will comment only that the plan includes some of the most innovative, reliable and state-of-the-art data integrity and audit mechanisms known to science in the context of the multi-center clinical trial.

We have responded openly and cooperatively to the requests of this subcommittee and its staff for documents, information and witness interviews and have similarly responded to requests from what I believe you refer to as the other body.

As has been reported in the press, the University convened an independent panel of nationally recognized experts to determine whether an investigation is warranted into possible scientific misconduct by several NSABP personnel. That panel is hard at work, and we are giving them all of the data and support that they need and want.

As you know, Mr. Chairman, and as we have discussed with the subcommittee staff, the University is bound by applicable HHS regulations to maintain the confidentiality of the misconduct inquiry and to preserve the due process rights of the individuals involved, who are represented by their own attorneys.

NSABP, NCI, NIH, HHS and the University of Pittsburgh personnel, in response to these important issues, have met and talked

by telephone innumerable times, exchanged detailed, voluminous information and worked continuously to get the facts, analyze the issues and meet all concerns. This work is ongoing, but I can report that very extensive and positive progress has been made.

Mr. Chairman, I will tell you frankly that over the past several months I have often asked myself what I could have and should have done to prevent the concerns that we are addressing today about NSABP's administration. That question has taken me down many pathways of self-examination, self-interrogation, and sometimes self-doubt.

Although I have many flaws, being timid is not one of them. Had I been motivated to probe the management of NSABP more deeply, I would certainly have done so. Why did I not?

The answer to this question why did I not is neither easy nor clear, and I do not yet have complete confidence in the answer even now. The answer, I believe, primarily relates to the culture of deference that has developed at universities over many, many years, if not centuries. The modern research university, although subject to strict accountability to government and the public, is primarily a highly decentralized system for research and teaching in which faculty, and especially well-established senior faculty, have very considerable autonomy.

Are we at the University of Pittsburgh behind the curve in this respect? I commissioned an informal survey of 20 leading American research universities to find the answer to this question. What I learned is that, with the possible exceptions of two universities, none of these leading institutions has in place a systematic, peer-driven mechanism for reviewing the adequacy of research administration by senior faculty. That finding did not surprise me.

As I pointed out in an interview some weeks ago to The New York Times, the time has come to give very serious consideration to changing this culture of deference. This matter requires thorough examination within the higher education community in general and the biomedical research community in particular. My guess is that this culture of deference, as Dr. Broder pointed out in his April 13th testimony to the subcommittee, made him hesitate to call upon the senior academic administration of our University when NCI did not get a satisfactory response from NSABP.

I will propose at the University of Pittsburgh, Mr. Chairman, a potent mechanism for peer review of the adequacy of administration by principal investigators, including senior faculty. We will use this new mechanism as a pilot program or model. Dr. O'Connor supports our efforts, and I expect that our faculty will support them as well when the merit of this initiative is presented.

Mr. Chairman, I also wish to say a word about research misconduct. We have taken very aggressive efforts at the University of Pittsburgh to deter such misconduct and to encourage the reporting of alleged research misconduct. We have had several cases that resulted in a finding of misconduct and on the whole handled them to the best of our ability, learning sometimes the hard way from our experience.

I might note that only two of our cases involved fabrication or falsification of data included in published research, like the case from Montreal that first brought the NSABP matter to our atten-

tion. It is extremely difficult and perhaps impossible to judge reliably whether a particular institution has more or less research misconduct than another institution. However, common sense suggests that there will be more misconduct proceedings at institutions that are alert to misconduct and report it competently, energetically and efficiently. Generalizations are hazardous about these matters and especially about the highly diverse and relatively few cases we have experienced at the University of Pittsburgh.

A legitimate question has also arisen whether it was sound policy to accept philanthropic funds from a pharmaceutical company to endow a proposed professorial chair when a product of the pharmaceutical company was being researched at the University and by the professor in whose honor the chair was to be named.

On the issue of conflict of interests and the Bernard Fisher-ICI Pharma Professorship in Surgery—which to the present day has never been fully funded or activated—we simply ask, as has the scientific community, that the government's standards in this evolving area be made clear and be applied prospectively, not retroactively. Researchers and the institutions at which they work can adjust to any reasonable standards, but it is counterproductive to judge them by standards not in effect now, let alone years ago.

Mr. Chairman, like virtually every other research University in the United States, the University of Pittsburgh, no less than NIH, Congress and the American people, is deeply concerned whenever administration of any of its programs falls short of sustained excellence, whether slightly short or far short. The facts are still not all in, but, like the National Cancer Institute, we acknowledge and are addressing in detail deficiencies and objectives for improvement.

The University of Pittsburgh's fundamental aim in relation to this matter is neither to defend nor to accuse but to determine dispassionately, fully and as speedily as feasible what happened, what can be learned from it and what remedial actions are appropriate and proportional to past performance and future commitment. To that end, we are hard at work, and we will remain at work until we have satisfactory answers.

Thank you very much, Mr. Chairman.

Mr. DINGELL. Thank you, Dr. Detre.

Dr. Herberman.

TESTIMONY OF RONALD B. HERBERMAN

Mr. HERBERMAN. Mr. Chairman and members of the subcommittee, I am Dr. Ronald Herberman, and I am pleased to be here today to talk about the National Surgical Adjuvant Breast and Bowel Project, the NSABP.

As interim chairman, I wish to briefly address its past, its present and its future. I have provided more detailed remarks for you to peruse at your leisure.

Mr. DINGELL. Without objection, those will be inserted in the record at the appropriate place.

Mr. HERBERMAN. Thank you, sir.

First and foremost, my goal as a cancer researcher as well as interim chairman of the NSABP is to see that this organization remains viable and effective. The NSABP must continue to develop

and implement innovative clinical trials, trials designed to advance the treatment and prevention of breast and colorectal cancer.

The NSABP is a most important research program. It needs to be preserved and restored to its full vitality.

Since March 30th, when I was asked by the University of Pittsburgh and by the National Cancer Institute to assume administrative responsibility for this program, I have felt it my obligation to be certain that what the NSABP accomplishes will truly be in the national interests. Primarily, it has to operate in the best interests of those women and men affected by breast or bowel cancer. In this regard, we have taken appropriate steps to move the organization forward and to restore confidence in the future of the NSABP.

Let me tell you about my initial reaction when I assumed responsibility for the NSABP. I found an organization under siege. There was widespread concern. This came from both the NCI and the public. It dealt with a variety of problems that the group had not adequately handled, but I also knew, as a cancer researcher—in fact, director of the Pittsburgh Cancer Institute—that this multicenter clinical trials group had a proud history. It had to its credit a series of pioneering and even ground-breaking discoveries relating to cancers of the breast, colon and rectum.

My immediate goal was to stabilize the program and to keep it on track. I believe that in a short period of only 10 weeks that we have been together our new team has accomplished a series of major steps towards restoring credibility. Yes, I believe we are getting the program back on track.

When I began my remarks I mentioned I would discuss the past, present and the future of the NSABP. Let me do that now with some specifics.

Past: You know about the deliberate data falsification problems at St. Luc Hospital in Montreal. They have been correctly and well documented.

The present: We are putting a system of data verification in place that will minimize the deliberate and also inadvertent errors.

Data falsification is reprehensible and cannot be tolerated, particularly when it may impact on patient welfare. However, in terms of effects on the results of clinical trials, the fact is that it doesn't matter if a mistake is deliberate or inadvertent. You must minimize it from happening.

Our system is totally unique for monitoring clinical trials at such a large number of institutions.

The future: First and foremost, it will involve the participants in verifying information about themselves. When someone volunteers to participate in a clinical study, that person will be shown a list of dates of key events that will determine eligibility. This might be the date of surgery or the date when a mammogram was performed.

This procedure is indeed revolutionary. As I just mentioned, something like this has never been incorporated into clinical trials before. If this had been in place previously, this rather simple step would have made it virtually impossible for the problems at St. Luc to have occurred.

So already we have taken the problem of misreporting information, we have addressed it and have come up with a unique, revolu-

tionary solution. This system, developed in cooperation with Westinghouse and Carnegie Group, will have real-time assessment of a patient's status and proposed treatment. It will immediately bring attention to deviations or inappropriate actions.

Let me show you this new system briefly in greater detail. In other words, we believe that this is the future. It will prevent falsification of data and prevent inappropriate procedures.

By the way, this system was unveiled earlier this week at the NSABP's annual meeting in Nashville. More than a hundred data managers from participating institutions enthusiastically endorsed the approach, and many of them were vying for being among the sites where the pilots would be carried out.

Let me read you the comments from one of the data managers at this meeting. "We have been requesting software like this for years to ensure quality data at our fingertips and for audits, will make data collection and data management efficient, will provide continuity and quality of care, great job done in 6 weeks."

Much of the details of this system have been already developed, and this has been done in close consultation with cancer survivors. We have put together an advisory committee to help us in this regard, and I will leave for the committee's interest a videotape which will show some of the process by which the cancer survivors helped us with this important process.

Mr. DINGELL. Thank you, Doctor, the committee will receive that, and we thank you.

Mr. HERBERMAN. Thank you, Mr. Chairman.

Another value of this system is the more complete informing of clinical trial participants about their disease, their proposed treatments and possible consequences. A customized notebook will be prepared for each patient electronically which will include information from the NCI's PDQ system and will be tailored for each woman's individual problems and the proposed treatments so that each participant on a clinical trial will be fully informed.

You will notice that this is in a loose-leaf fashion. This will be updated at every visit of the participant to see the doctors and the NSABP.

A third issue deals with the drug tamoxifen. There is a risk in taking most drugs. An NSABP study itself has demonstrated a relationship between the use of tamoxifen for treating breast cancer and the development of uterine cancer. There were some delays in ascertaining that deaths were a result of uterine cancer. Ways have to be found to diagnose uterine cancer early to prevent progression and even death.

Since assuming responsibility we did two major things in this regard. First, we established an independent data and safety monitoring question. This meets regularly and reviews all information about side effects from any treatments. This group will have the power to make appropriate corrective action or even stop the trials until problems are solved.

Second, we have developed a protocol that mandates regular uterine examination on all new participants in tamoxifen trials. For women already enrolled on a tamoxifen trial, they must at least be told about the recommendations for such regular monitoring.

By the way, previous NSABP studies have clearly indicated the benefits from the use of tamoxifen. The NSABP trials have shown that tamoxifen is highly effective in preventing recurrence of the original breast cancer. At the same time, the studies demonstrated that tamoxifen went a long way in preventing a new cancer in the opposite breast, and, in fact, this important finding laid the foundation for the breast cancer prevention trial that is currently being performed by the NSABP.

In summary, the NSABP has certainly had its share of challenges—there is no doubt about that—but things are back on track. An effective quality assurance program is already in place. In fact, our new system of data verification, I believe, is a major breakthrough.

The formation of oversight and also data and safety monitoring committees add greater credibility than ever before. We have put steps into place to streamline headquarters operations and to develop open communications with patients and with the public. The momentum is started so that the NSABP can continue to be the high quality organization it was meant to be. I can assure you that the NSABP is indeed back on track.

Thank you very much, Mr. Chairman.

[Testimony resumes on p. 157.]

[The prepared statement of Dr. Herberman follows:]

STATEMENT

OF

DR. RONALD B. HERBERMAN
INTERIM CHAIRMAN
NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT

Mr. Chairman and members of the Subcommittee, thank you for permitting me to appear before you today and provide my views as the Interim Chairman of the National Surgical Adjuvant Breast and Bowel Project ("NSABP"), a position I have held for slightly more than two months. I also welcome the opportunity to answer your questions -- as I have in meetings with Subcommittee staff -- and to provide information.

By way of background and for the Subcommittee's information, I also serve as the Hillman Professor of Oncology and Professor of Medicine and Pathology at the University of Pittsburgh and as Director of the Pittsburgh Cancer Institute. The Pittsburgh Cancer Institute is one of twenty-seven federally-designated comprehensive cancer centers in the country. It is responsible for cancer research and care at the University of Pittsburgh Medical Center. Before joining PCI, I served at the National Cancer Institute for nineteen years. As a result of my work in these positions, I have extensive experience in clinically relevant cancer research, clinical trials, and research administration.

I am highly honored to serve as Interim Chairman of NSABP, especially at this critically challenging time. Although recent events have understandably focused attention on NSABP's past administrative deficiencies, I nevertheless think it appropriate to approach the leadership of this organization as an act of stewardship over an invaluable national resource that was

founded and nurtured by the dedication of many others: Dr. Bernard Fisher, founder and former Chair of NSABP, who has dedicated his entire professional life to eradicating the scourge of breast cancer; Dr. Carol Redmond, a renowned statistician who has created and managed the quantitative foundation of the NSABP's research; the many members of their staff at the University of Pittsburgh and approximately 5000 researchers at almost five hundred other facilities participating in NSABP trials, who -- with some regrettable exceptions -- have conducted the massive research operation that is NSABP with a high level of dedication and professionalism; the federal government and taxpayers who provided the financial resources for this endeavor; and, most importantly, the 50,000 or so women who have participated in the numerous NSABP clinical trials that have so markedly contributed to our understanding of appropriate treatments for breast cancer.

Among the major and ground-breaking innovations that resulted from the efforts and dedication of these contributors are studies that have: 1) provided evidence supporting the use of breast conservation surgery as an alternative to radical mastectomy, the disfiguring surgery that was previously the standard procedure in cases of breast cancer; 2) demonstrated an appropriate role for chemotherapy in the treatment of primary breast and colon cancer; and 3) demonstrated the value of the drug Tamoxifen for the treatment of breast cancer and the prevention of second primary cancers. It is on the foundation of

these and other significant scientific findings that we now work to build a stronger and more accountable NSABP.

Since assuming the interim chairmanship of NSABP a little more than two months ago, I have been engaged more than full time in that work. A wide variety of issues and tasks have arisen on a number of fronts during that time period. As the interim chairman of NSABP, however, I have primarily focused on two key priorities. First, one of my main tasks in the last two months has been to develop open communications and make concerted efforts to restore the confidence of patients and the public in NSABP clinical trials and, derivatively, in clinical trials generally. Second, and in service of the first priority, I have been working, together with Dr. Donald Trump, Interim Executive Officer of NSABP as well as Deputy Director of the Pittsburgh Cancer Institute, to understand the administrative and other problems that exist at NSABP and to respond by developing detailed plans to ensure that these problems cannot occur in the future.

Let me first mention generally the types of problems we have identified. As made clear by the entire St. Luc episode -- and several other, less dramatic, episodes that have subsequently come to light -- NSABP unfortunately suffered from a number of deficiencies in quality assurance and also administrative and reporting lapses in the face of problems that were detected in audits of institutions outside Pittsburgh that enroll patients in NSABP studies. On some occasions, for example, questions

concerning the eligibility of patients to participate in various NSABP clinical trials were identified at the time of an audit but not properly resolved. Most of the identified problems may be grouped into two categories, one focused on several of the almost 500 institutions around the United States and Canada participating in the clinical trials, and one reflecting deficiencies in the NSABP Headquarters:

1. Deliberate or inadvertent errors in data affecting eligibility or other important aspects of the studies. Whether such errors are deliberate or a result of sloppiness in record keeping, they detract from the research and must be minimized; and

2. Slow or ineffective handling of the problems once they are detected by Headquarters staff.

Each such deficiency is of urgent concern. Let me stress, however, that nothing we have discovered during this period of intense scrutiny has provided any basis to doubt the fundamental findings of NSABP's various ground-breaking studies. In fact, various independent clinical trials and also reanalyses of the NSABP data -- both within and without NSABP -- have confirmed all of the major conclusions from those studies.

In addition, as NCI has known for some time, NSABP had in the last year fallen significantly behind schedule in performing the audits of institutions. While there may have been some plausible reasons for this problem, including the shift to implementation during the last year of a new and improved NSABP auditing system, we simply cannot tolerate gaps in verification of information and practices at participating institutions. In light of the particular concerns that have been expressed concerning the gathering and handling of information relating the use of Tamoxifen to increased risk of developing endometrial cancer, we have also been re-examining intensively the entire NSABP system for identifying and reporting adverse drug reactions that may be experienced by patients enrolled in NSABP protocols.

These are some of the types of problems we have identified in our efforts to make NSABP a stronger and more accountable research organization. In response to these problems and others, however -- and in the midst of crushing demands for information from various government entities and the press -- we have in the space of two short months implemented a number of significant structural and administrative changes that we believe will both address these problems directly and restore the confidence of participants in NSABP clinical trials, the breast and bowel cancer community, the scientific community generally, and the public at large. These actions and proposals for further action are explained in detail in the "NSABP Plan for Corrective Actions" that was submitted to NCI on May 24. A copy of this

Plan has been provided to the Committee for its information. I summarize here some of the key components of this plan.

Working closely with Dr. Samuel Broder, Director of NCI, Dr. Bruce Chabner, Director of NCI's Division of Cancer Treatment, and other NCI officials, we have established the ***NSABP Oversight Committee*** as an external advisory group. Members of the Committee include experts in large-scale, clinical cancer trials. Of particular significance, moreover, the Committee includes two lay members who serve as advocates for breast cancer patients and survivors: Amy Langer, Executive Director of the National Alliance of Breast Cancer Organizations, a member of the Board of Directors of the National Breast Cancer Coalition, and a breast cancer survivor; and Dorothy Raizman, an attorney who is a recognized authority on medical records and the communication of information within and throughout the medical system. The NSABP Oversight Committee is advising me on reorganization of the NSABP leadership structure, and will continue in place at least until the NSABP is stabilized and functioning more effectively.

With the assistance of the NSABP Oversight Committee, we have proposed a plan for a new ***NSABP leadership structure***. We are working on revisions of the NSABP constitution and bylaws that will shift a good deal of responsibility for management of NSABP from the group Chair to a reconstituted Executive Committee. The Executive Committee membership will be more broadly representative of all group constituencies than the current Executive Committee. Following reconstitution of the

Executive Committee, that body will nominate candidates for a new permanent group Chairman, and this important step will be followed by an election by the membership of the group, and approval of the selection by the National Cancer Institute.

A major goal of our revised leadership structure is to ensure ***greater participation by the health care providers and researchers in local NSABP centers in the design and execution of research protocols***. I hasten to note that, even under the former management structure, protocol design committees and the NSABP group meetings have generally provided excellent opportunities for group-wide participation in protocol design. Our proposed management structure will further enhance membership involvement by establishing standing disease-specific (breast or colorectal) committees, each with a chair empowered to review continuously the status of ongoing trials, solicit group-wide and ad hoc external input, and guide development of new protocol concepts. These committees will be responsible to the Executive Committee, which, as noted, will itself have broader membership and more inclusive group representation than under its current structure.

We have also established a ***Data and Safety Monitoring Committee***, the membership of which is completely independent of NSABP. The primary responsibility of this Committee is to review interim analyses of outcome data and to recommended changes in -- or termination of -- studies based on these analyses. The Committee will also review toxicity data, major modifications of studies, NSABP handling of scientific misconduct, NSABP quality

assurance, and consent form issues related to toxicities. Included as a member of this Committee is Kay Dickersin, Ph.D., Department of Ophthalmology, University of Maryland, who is a breast cancer advocate and survivor, with considerable expertise in clinical trials and epidemiology.

In consultation with NCI and experienced auditors from other cooperative groups, we have also developed an improved on-site monitoring and quality assurance program. Under these ***new audit procedures***, an institution will be notified four weeks in advance of a proposed audit, and will be informed two weeks in advance as to which cases are to be audited. These cases are randomly selected, and additional cases are identified on site at the time of the audit. Document review will occur on site, rather than at NSABP as under the former system. Each audit team will include an independent member and NSABP group members will be involved in the actual performance of the audits. To assist in the implementation of these new procedures, we have subcontracted with a consulting firm experienced in the auditing of oncology trials.

NSABP will notify the Clinical Trials Monitoring Branch ("CTMB") of NCI of any major deviation within 24 hours of discovery, and will send by facsimile the preliminary audit finding within 24 hours of completion of the audit. Within seven days of the auditors' return and after review by the Executive Officer, NSABP will transmit an audit summary to NCI and the audited institution. The institution will then be given 20 days

to respond. Within 30 days of the preliminary report and after approval by the Quality Assurance Committee, a final report containing the Executive Officer's recommendations will be sent to NCI and the institution. All institutions will be at risk of annual audits, and will be audited at least once every three years.

NSABP has proposed a schedule that will eliminate the back-log of audits by April 1, 1995, with highest priority given to institutions with large numbers of accruals, previously recognized problems, or a gap of more than three years since the previous audit. A review of past audits will be used to identify outstanding issues and priorities for future audits. NSABP will provide NCI semi-annually an updated list of institutions to be audited within the next six months. New procedures are being developed to provide for timely auditing of low-accruing institutions and small affiliates.

In response to problems identified in past audits, NSABP has assisted NCI in organizing re-audits, followed up on identified deficiencies, and taken significant corrective measures. In addition, we have initiated a broad scale review of all previously conducted audits -- and NSABP's handling of deficiencies identified by those audits -- to further ensure that *all* questions involving quality assurance are appropriately resolved.

We have also been examining ways to increase the reliability of information at the time it is initially entered into the NSABP process. Calling upon existing relationships with the Westinghouse Electric Corporation's Science and Technology Center and Carnegie Group, Inc. Dr. Trump and I have worked to generate new processes for handling data monitoring and quality control issues. I should note that we began to develop these processes over a year ago, well before the current controversy over NSABP arose. One important new procedure will involve patients -- who likely are in the best position to verify certain information -- in quality control procedures incorporating important patient history dates into the consent form for patient verification. The University of Pittsburgh has also been working with Westinghouse and the Carnegie Group to develop a prototype system for data confirmation and quality control, which was demonstrated earlier this week to investigators and data managers at the NSABP group meeting in Nashville. Improvement of this information process continues, and a pilot test and verification of its effectiveness are planned.

One of our primary concerns is to ***increase the involvement of breast and colorectal cancer survivors and their advocates in the NSABP***. A comprehensive plan to achieve this goal is being developed and will be presented to NSABP members at our group meeting later this month. Under this innovative plan, representatives of these groups will: 1) attend and participate in each NSABP membership meeting; 2) serve on protocol

development committees; 3) serve on focus groups to provide input on protocol design, informed consent documents, and audit procedures; and 4) participate in the development of plans for assessing such issues as effects of clinical trials on quality of life, compliance of patients on clinical protocols, and psychological aspects of clinical trials. We will also develop a procedure to inform participants in a trial and their families about the results of a trial as they are published. We hope to establish a close and ongoing partnership between patients and their physicians, and to ensure that patients are fully educated about the clinical trials in which they participate.

Let me also mention some specific actions we have taken in ***response to St. Luc*** falsifications and the questions about whether those were adequately disclosed. NSABP officials previously had determined (in July 1991) that the falsified data did not affect study outcomes, and had given a presentation to NCI officials in March 1992 on their statistical reanalysis of data from four NSABP trials, excluding falsified data from St. Luc Hospital. Although NCI and ORI had asked NSABP to prepare a reanalysis for publication immediately following the conclusion of ORI's investigation into St. Luc, the reanalysis was not assigned the priority that it merited. NSABP submitted the formal manuscript to NCI on February 8, 1994.

On March 17, 1994 Dr. Fisher notified the New England Journal of Medicine ("NEJM") that papers published in that journal concerning three NSABP trials contained falsified data

from St. Luc. NSABP had mistakenly decided not to notify NEJM of the ORI findings earlier because those findings had been published in the Federal Register, because Drs. Fisher and Redmond were preparing a formal paper for submission to NEJM, and because the falsified data did not affect the study results. The University acknowledged that this was a mistake in a March 28, 1994 letter to the editor of NEJM. On March 25, after NCI's review, the paper reanalyzing data from the three trials was submitted to NEJM for publication.

On March 30, Dr. Fisher notified in writing all other journals that had published articles including fraudulent St. Luc data since 1991. NSABP withdrew manuscripts including tainted data that had been submitted or were in press. On April 7, 1994, we sent all principal investigators a summary of ORI's findings regarding St. Luc and a model letter to patients reassuring them of the validity of the study results and acknowledging the misperception created by NSABP's delay in publicizing the problem. On May 6, 1994 I wrote to the editors of all affected journals and affirmed NSABP's commitment to reanalyzing the trial data and confirming the studies' validity.

NSABP currently is preparing a manuscript describing the reanalysis of all affected trials. This reanalysis will be provided for NCI's review by June 30, 1994 and submitted for publication upon NCI's approval. A detailed description of the reanalysis appeared in a Technical Report distributed at our NSABP meeting (which was held over the last several days) and is

being made available to journals that have published reports including St. Luc data. Each if these journals will also receive notices of the formal, published reanalysis. At our recent NSABP meeting, we had an extensive discussion of the St. Luc incident, which I believe served to educate NSABP physicians, data monitors, and support staff about the St. Luc problem, the ethical and legal consequences of scientific fraud, and NSABP's new procedures for preventing and detecting data falsification. A letter describing the St. Luc problem has been developed in consultation with breast cancer advocates and sent to a wide range of individuals and organizations.

With respect to problems at other institutions, I think it is important to stress that none of the other cases we are examining have been determined to involve the type of deliberate and systemic falsifications that were identified at St. Luc, although investigation is ongoing. That does not, of course, diminish in the least the need to address data integrity issues, for we should strive to eliminate all error -- whether deliberate or inadvertent -- from our data set.

In connection with the discovery of evidence of possible scientific misconduct at St. Mary's Hospital in Montreal, NSABP has worked to correct the problems leading to a delay in reporting that evidence to NCI, and has provided NCI with information and assistance in re-auditing St. Mary's. ORI's investigation into evidence of scientific misconduct at St. Mary's is expected to conclude in the near future.

Administrative problems that have been identified during audits of Louisiana State University ("LSU") and Tulane University led to suspension of these institutions that month, prior to the general suspensions of NSABP institutions. These problems have been identified to the principal investigators at LSU and Tulane, whose responses and proposals for solving the problems will be addressed. Dr. Trump as Interim Executive Officer is reviewing these responses and together with NSABP staff will determine whether accrual at these sites should be resumed. We have also been working with NCI to address problems relating to Memorial Cancer Research Foundation in Los Angeles and its principal investigator, Dr. David Plotkin, and South Nassau Community Hospital.

We are well aware that NCI has perceived an unresponsiveness or inadequate responsiveness from NSABP in the past, particularly in the administrative realm. That perception, whatever the basis for it, is destructive of the close working relationship with the funding agency that is necessary to the conduct of federally sponsored research. We have taken very substantial and concrete steps to ensure responsiveness to NCI, and to prevent such a perception henceforth.

I should also mention, as has been reported in the press, that the University has initiated a scientific misconduct inquiry relating to events and actions at NSABP. A highly distinguished three-member panel has been convened. Each of the panelists is a nationally recognized authority, based at another

institution, holds no position at the University of Pittsburgh, and is independent of both the University and NSABP. The purpose of the preliminary inquiry is to determine whether a formal investigation of this matter as a scientific misconduct case is warranted. Fairness to the respondents in that inquiry compels me to refrain from further comment.

As I said at the outset, I view my service to NSABP as an act of stewardship over a valuable national resource. It is my firm belief that the actions I have described, and the path we are now on, will not only preserve that resource from deterioration, but will also nurture and rejuvenate NSABP so that it may continue and expand its service to the women of this nation for years to come. I am pleased that we have made such significant progress that we were permitted last week to announce that NSABP will begin to accrue patients once again into its vitally important clinical trials. I look forward to working with the Members of this Subcommittee, NIH, NCI, and breast and bowel cancer patients and their advocates, to ensure that this step is only the initial evidence of the successful reorganization of the NSABP.

I would be pleased to answer any questions you may have.

Mr. DINGELL. Gentlemen, the Chair wants to thank you for your very fine statements.

Dr. O'Connor, as you indicated, the committee has sharp teeth, and we don't always like to use them on people, but occasionally these things happen. I want to commend you and you, Dr. Detre, and you, Dr. Herberman, for, first, fine statements; second of all, to tell you that the staff and I have appreciated the way that you have worked with us and we have worked with you to address the concerns of the committee and to tell you that, from your statements and from what we have seen as we have worked moving towards these hearings, my belief that the process of scientific review and supervision and auditing will move much forward because of the good work which you have done and are doing, and we commend you for that. Thank you.

Mr. O'CONNOR. Thank you.

Mr. DINGELL. The Chair does have some questions, and the Chair advises that the Chair will be recognizing members for 10 minutes rather than 5 in order to address the questions that we have before us.

I would like to observe to you, Dr. Detre, that I come from a part of the country where accents are common. And we are not only comfortable with them, but we think that our best and most productive people very frequently have accents. And we are comfortable with them, and we rejoice that we have people who have accents who can make meaningful and good contributions. So I am comfortable with it, and I hope you are, too.

Mr. DETRE. Thank you, sir.

Mr. DINGELL. First of all, Dr. Detre, since this situation unfolded the University of Pittsburgh has initiated a number of separate reviews or investigations which have been referred to in the comments of yourself, Dr. O'Connor and Dr. Herberman. Without discussing the questions of scientific misconduct in that investigation that is currently under way, could you describe in general what you found regarding the management and administration of NSABP?

Mr. DETRE. Yes, Mr. Chairman, that is a very important question. Literally every component of the NSABP functions reasonably well, but the coordination among the various functions showed considerable deficiencies. This, in turn, led to delayed reporting in some instances or lack of reporting in others.

Mr. DINGELL. Now, Dr. Detre, what would you say went wrong with management and administration of NSABP?

Mr. DETRE. Mr. Chairman, I don't think I can be more precise about it except to say that the administration of NSABP needs some reform. Reform which would ensure, as Dr. Herberman pointed out, that the database for clinical research begins with the patient, that there is a clear trail following the data through the various phases of the treatment trial and that the reporting relationships are clearly defined and that an independent mechanism is in place to ensure that not just the audits are done but audit reports arrive through the proper agencies at the proper time.

Mr. DINGELL. Dr. Herberman, we understand that your own investigations have revealed that NSABP was violating its own constitution with respect to the recruitment and the selection of participating sites. Could you please describe what you found in this

regard? Specifically, how was this process supposed to work, and then how did it, in fact, work?

Mr. HERBERMAN. The constitution that currently governs the NSABP is a rather old document. It is dated 1969 and, as best as we can determine, has had very little updating since then. We are currently working on that very matter and will soon have a new and revised constitution.

The description in the constitution, as the original document which is now undergoing extensive revision, was that member institutions would need to be voted on by the membership of the NSABP. For the last number of years, at least, this has not been the practice, but rather there was an administrative mechanism within the headquarters operation for one of the staff to collect all of the necessary documents and to essentially decide whether all the documents were in place and, if so, to approve an investigator or even an institution for membership in the NSABP.

Mr. DINGELL. Now, Dr. Herberman, what is your own view of the effect that this violation of the NSABP's own constitution had on the selection of sites and their ability to produce verifiable data?

Mr. HERBERMAN. Well, the NSABP has grown to be a very large and complex organization. It has almost 500 sites which vary in their nature and their quality. I believe that processes need to be in place to ensure the training and the quality of each of the institutions that participate and procedures are now being put into place to be sure that the smaller institutions and the ones that are likely to accrue small numbers of patients will affiliate themselves with larger institutions in their region so that there can be a direct help to be sure that the proper procedures are always carried out.

Mr. DINGELL. Now, Dr. Herberman, can you tell us what you have learned about the methods by which NSABP reimbursed its sites for patient recruitment? Specifically, were the majority of the sites paid for accrual patient by patient?

Mr. HERBERMAN. There have been a variety of mechanisms, Mr. Chairman, for reimbursing institutions that participate in the clinical trials. There currently are 11 institutions that receive grants directly from the National Cancer Institute for their participation in NSABP clinical trials.

The much more common mechanism at the moment is the disbursement of money through purchase service agreements that is administered by the headquarters at the University of Pittsburgh. For the purchase service agreements, the mechanism essentially is a per capita payment for each participant entering onto a clinical trial.

Mr. DINGELL. Now, Dr. Herberman, is it not also true that for those sites payments were routinely made before eligibility for the patient had been confirmed and long before the patient entered follow-up?

Mr. HERBERMAN. Well, sir, my understanding has been that the practice is that a trigger for payment for a participant would occur at the time of randomization. A patient would not be randomized until checks for eligibility had been completed. But if there subsequently, after randomization, was a determination of ineligibility, there was not a mechanism in place to recover such funds. There also was not a mechanism for adjusting the funds relating to the

extent or the quality of the follow-up. The payment was made at the beginning, with the presumption being that this was funding for the entire process, the entry and the follow-up of each participant.

Mr. DINGELL. Two questions, then. Did this contribute to eligibility discrepancies? And did it contribute to follow-up delinquencies?

Mr. HERBERMAN. It is hard to determine an answer to that, Mr. Chairman. I believe that the very vast majority of the participating institutions have been extremely conscientious in carrying out all aspects of the clinical trials that they participate in.

It is also important to note that the amount of funding that was coming from the Federal Government did not provide full funding for all of the aspects of the clinical trials that institutions participated in. I am convinced that the primary motive for institutions and the physicians associated with them to participate was their enthusiasm about the important work that was being carried out and not directly linked to the payment mechanism.

Mr. DINGELL. Now, Dr. Detre, did NSABP ever attempt to recapture funds for patients ultimately proven to be ineligible or unavailable for follow-up?

Mr. DETRE. Not to the best of my knowledge, Mr. Chairman, but I may be in error.

Mr. DINGELL. Could you give us—could you tell us why?

Mr. HERBERMAN. Mr. Chairman, if you would permit me, I think I might answer that question. This came up for some discussion when the National Cancer Institute officials visited the University of Pittsburgh last month.

What was pointed out was that, because only partial reimbursement for the total costs of the trials were being performed, there was a general feeling that the amount of money that was being disbursed was still less than the total cost that an institution would have, particularly because the proportion of ineligible patients at any given institution has tended to be relatively low.

Mr. DINGELL. Thank you, doctor.

The Chair notes that I have used about all the time that I should at this particular time so the Chair is going to recognize my good friend from Colorado, Mr. Schaefer.

Mr. SCHAEFER. Thank you, Mr. Chairman.

I would just like to, at the outset, reflect what the chairman stated to you gentlemen about the cooperation with our subcommittee staff in trying to find all the answers that we and the American public really needs to know on this matter.

Earlier this week, Dr. O'Connor, the NCI announced it was opening competition for the management of NSABP. Is the University of Pittsburgh going to compete in this? Up to this point it had just been a given, as I understand it.

Mr. O'CONNOR. We certainly do intend to compete, Congressman Schaefer.

Mr. SCHAEFER. Now, if you do compete in this, what specific approach would you take that differs from the past management of NSABP?

Mr. O'CONNOR. I think Dr. Herberman will be in a better position to fill in some of those details, Congressman, but I will say

that we have aggressively pursued an alteration of the organization so that it will be both more effective in monitoring and in communicating when that needs to happen. But I think Dr. Herberman is probably in a better position.

Mr. SCHAEFER. Doctor, I know both of you have mentioned changes in your testimony, but do you want to amplify a little about it?

Mr. HERBERMAN. Yes. Thank you for the opportunity to respond, Congressman Schaefer.

As I briefly described in my testimony, we have very rapidly put into place an extensive series of corrective steps and I believe important improvements in the way that the NSABP will operate. Because of this intense focus on these problems and giving virtually full-time dedication not only on my part and Dr. Trump's part and several other staff members, I believe that we are now uniquely suited to be able to stabilize the group and to keep its important programs on track.

We certainly intend to continue this progress and particularly with the development of these innovative data management and quality assurance programs. We believe that this is the best prospect for the NSABP to function at the highest possible level.

Mr. SCHAEFER. It seems to me that in the past, with the NCI automatically having the University of Pittsburgh do it, there might have been some complacency out there and maybe this contributed to what occurred. I applaud you for taking some new steps.

What, may I ask, would Dr. Fisher's role play if the University of Pittsburgh were to get this particular grant?

Mr. HERBERMAN. Congressman Schaefer, the one thing that is clear, I believe, is that there is no plan for Dr. Fisher to resume administrative responsibilities for the NSABP or to have direct-line authority for any aspects of the program.

Mr. SCHAEFER. Do the rest of you gentlemen concur with this?

Mr. O'CONNOR. That is correct, Mr. Schaefer. Dr. Fisher has done some heroic research in the past and will probably continue to be able to do that, but he will not have administrative responsibility in NSABP.

Mr. SCHAEFER. You stated, and I find it reassuring, that NSABP's research findings continue to be sound, and charges of deficient administration are not adequately answered by merely asserting that the research remains valid. I gather that then you would dispute those who characterize the problems at NSABP as trivial or nonevents?

Mr. O'CONNOR. Congressman, I don't think that falsification of anything is ever acceptable and particularly when it deals with the public health.

Mr. SCHAEFER. So it would not be trivial?

Mr. O'CONNOR. It is not trivial, sir.

Mr. SCHAEFER. Thank you.

Mr. Herberman, I am encouraged in your testimony concerning the steps you are taking to improve the quality control system of NSABP. It is, of course, prospective in nature. What plans do you have to address the backlog of audit reports and ensure that the information currently in NSABP's possession is accurate?

Mr. HERBERMAN. Congressman, this is a matter of great concern to us. Verification and assurance of the quality of the data, I believe, is of primary concern. We are working assiduously to develop an audit schedule in which all of the institutions that had not been audited during the requisite 3-year period will be audited within the very near future.

In addition, all of the institutions in which we have detected problems in previous audits will be given the highest priority for a reaudit and more attention. In order to be sure that this process moves as expeditiously as possible and to catch up, we have been making arrangements with a contractor organization with experience in clinical trials related to cancer to help us with this matter, at least until we can catch up in the backlog.

Mr. SCHAEFER. Two questions. How many of these programs have you identified as being problems? And have you any idea what this is going to cost?

Mr. HERBERMAN. One of the things that we commissioned shortly after I took on responsibility for the NSABP was to go back over the last 4 years of all the audit reports. This was over 120 audits. Among those we have determined there are about 11 that had significant problems that might affect eligibility or have important impact on the clinical trials. These will be the ones we will focus on particularly.

Mr. SCHAEFER. That is a pretty high percent. We are talking 9, 10 percent.

Mr. HERBERMAN. It was about 10 percent. These are serious concerns, and we will deal with these expeditiously.

Mr. SCHAEFER. Again, you don't have any idea of what the cost is going to be involved in this? You may not have at this point, and I understand that.

Mr. HERBERMAN. I really don't have figures on the costs at my fingertips.

Mr. SCHAEFER. And I understand that.

You are the interim chairman of NSABP. What is the time frame on the permanent chairman? Will that be this fall sometime?

Mr. O'CONNOR. Congressman Schaefer, if I may, we have just established a search committee of approximately five people, and I am going to chair that search, and we hope to have the individual identified by late summer, early fall.

Mr. SCHAEFER. Good. Dr. Detre, do you believe the peer review system is adequate when it comes to administration oversight?

Mr. DETRE. Would you repeat the question, Congressman Schaefer?

Mr. SCHAEFER. I would be happy to. Do you believe that a peer review system is adequate when it comes to administration oversight?

Mr. DETRE. I don't believe so, Congressman Schaefer. I believe that there must be some additional institutionally based mechanism to guarantee that the administration is adequate for the task at hand, particularly in such large-scale clinical trials as the NSABP which over the years literally included tens of thousands of patients at 400 or 500 different sites.

Mr. SCHAEFER. In advocating the guidelines when it comes to accepting philanthropic funds from pharmaceutical companies, are you advocating setting up Federal guidelines for this?

Mr. DETRE. Mr. Chairman, our conflict of interest guidelines are in place at the University of Pittsburgh. At this point—and that I believe is the national standard—we require our faculty to report any funds that come from pharmaceutical companies.

Mr. SCHAEFER. Mr. Chairman, I would yield back.

Mr. BROWN [presiding]. Thank you, Mr. Schaefer.

Dr. Herberman, we have reviewed your May 12th of this year draft report of your review of NSABP recent audits for several dozen sites with major discrepancies. There was no indication that those discrepancies had been resolved or that the potential irregularities further examined. How did this occur? Why was this occurring at NSABP?

Mr. HERBERMAN. I think that is an important question, Congressman Brown. I really don't have a complete answer to what the reason for these lapses might have been. We are very concerned about it, and I can assure you that now that I am aware that these—some of these reporting loops are open, we are taking steps to immediately close them.

Mr. BROWN. What do you intend to do? What are you going to do to follow up on these reports?

Mr. HERBERMAN. Well, because we were not entirely certain which of some of these reports had been communicated to the NCI, we have sent all of them to the National Cancer Institute so they have been fully informed.

In addition to that, we are in the process of notifying each of the principal investigators related to these institutions. It is, frankly, difficult for us to determine from the files which principal investigators were informed and which were not informed about the problems. And to ensure that everyone who needs to know is informed, we will inform all of them.

Mr. BROWN. Why weren't these principal investigators informed?

Mr. HERBERMAN. Again, Congressman Brown, it is not clear to me what was the basis for the lapses in the past. I, frankly, have focused my attention not so much on determining the why but the nature of the problem itself and what needed to be done for corrective action, and this is what I believe we have done rather thoroughly in the last 10 weeks.

Mr. BROWN. NSABP's own audit report cites the possibility that patients have been given incorrect or inappropriate treatments for medical conditions or their care has otherwise been altered or compromised. What responsibility does NSABP have to look into the well-being of these women?

Mr. HERBERMAN. Well, Congressman Brown, this is an issue of greatest concern to us. Any actions or inactions that would affect the welfare of patients is, of course, of first priority and concern. It is difficult in many cases well after the fact when an audit is performed, which is often 2 or more years after a patient has been treated, to take a really effective corrective action for that particular woman. This is one of the reasons why we are putting this new system in place, so that we can get immediate, real-time assess-

ment of problems and correct them while the woman is still under treatment so the appropriate treatments can be provided.

Mr. BROWN. Dr. Detre, do you have anything to add to that?

Mr. DETRE. I am not, of course, an oncologist, Mr. Chairman, Congressman Brown. I am just an ordinary physician who is a neuropsychiatrist by training.

I would say that in those instances that the questions about eligibility for trial for inappropriateness of treatment, NSABP under a new organization will provide for the reexamination of these women to provide them with the best possible advice.

I might add that while there may have been problems on eligibility, which is inexcusable, or treatment, which is inexcusable, it does not necessarily mean that there are serious consequences of these deficiencies. These can be determined only by thorough examination of the patients and proper consultation and advice to them.

Mr. BROWN. When will you have done that?

Mr. DETRE. As soon as all of these problems are identified.

And that process is ongoing—Dr. Herberman probably will tell you when all these audits are finished. Individuals who if for any reason whatsoever may not have received proper care or were enrolled in trials for which they were not eligible have to be examined by experts and not on site but independent experts.

Mr. BROWN. Dr. Herberman, tell us, if you would, if you would identify the sites which had the most significant audit discrepancies. Would you identify those for us?

Mr. HERBERMAN. Certainly. I think the sites that had the most significant problems in fact are the ones that have come to the public attention. In addition to St. Luc Hospital in Montreal there is a second hospital in Montreal, St. Mary's, that my understanding from Dr. Broder there is a determination of some deliberate alteration which, again, is of grave concern to us, particularly as it has occurred in the prevention trial.

Beyond that, the institution where there have been, I believe, the most serious concerns or allegations brought forward has been at Memorial Cancer Research Foundation in Los Angeles. In addition, there have been a few other sites in which there have been multiple instances of what I would characterize as sloppiness in the handling of the records and the clinical trials data, and for those this would include particularly LSU and Tulane in New Orleans and South Nassau Communities Hospital in Long Island.

Mr. BROWN. The Los Angeles site—apparently, there was an unmailed audit report. Can you tell us about that, the United Memorial Cancer Foundation?

Mr. HERBERMAN. We first learned about the issue at Memorial in Los Angeles after it was reported in the newspaper and when Dr. Plotkin, the principal investigator there, requested the National Cancer Institute to do an audit. I spoke immediately both before the audit and while the audit was going on with NCI officials and determined that there were serious enough problems to place the principal investigator, Dr. Plotkin, on—suspend him from his participation in the clinical trials.

Why this prior audit report which described a number of discrepancies in 1990 was not mailed is very difficult to determine. As best as I can surmise, the intention was to perform a reaudit and

to provide that letter about the prior problems to Dr. Plotkin at that time, but that reaudit was not performed.

Mr. BROWN. You had earlier said there were 11 sites. You mentioned, I believe, 6. You mentioned two in Montreal, two in Louisiana, one on Long Island and the Los Angeles site. What are the other five?

Mr. HERBERMAN. I don't have the list of the others in front of me, but there are several others. We could provide this to the committee almost immediately.

Mr. BROWN. Would you please submit that to us? Is one of those Pittsburgh?

Mr. HERBERMAN. No, sir.

Mr. BROWN. What is the nature of the most serious discrepancies that you found in the audit reports? Tell me a little bit about the nature of them.

Mr. HERBERMAN. Well, the type of discrepancies or problems vary rather widely. The most serious one I would characterize relates to information that would affect eligibility of patients entering onto a trial.

A second area of considerable concern has been the documentation of the informed consent and exactly when the informed consent was administered and signed by the patient.

In addition to that, there have been some questions or possible errors related to laboratory values of patients and some other issues about follow-up, but most of it, I would say, was in the area of eligibility and consenting.

Mr. BROWN. Dr. O'Connor, for a moment, you had stated in your opening statement, "I accept responsibility for past administrative shortcomings and deficiencies of the NSABP project, which is headquartered at the University." Tell the subcommittee exactly what you mean by that, "accepting responsibility."

Mr. O'CONNOR. I will be happy to do so, Congressman Brown.

I accept the responsibility of putting together an administrative team with Dr. Detre and Dr. Herberman which will review the administration of the NSABP grant and bring it up to an administrative quality that is demanded by the kind of work that it undertakes.

Mr. BROWN. The situation is going to be costly in at least three different ways. One is the cost to the government for investigating and auditing this whole situation; second is the cost to the University for conducting its various reviews and inquiries, and your coming here and all that; and third is the cost of recruiting patients whose data was found, for a variety of reasons, to be unusable.

Does Pittsburgh intend to reimburse the Federal Government for the cost incurred in this whole investigation of this matter?

Mr. O'CONNOR. It certainly is a point that is under discussion, Congressman Brown, and I think it will continue to be under discussion.

Mr. BROWN. Under discussion among whom?

Mr. O'CONNOR. Well, it certainly has been a discussion with NCI.

Mr. BROWN. You will make the final decision, is my understanding, at the University of Pittsburgh on whether or not the University agrees without any request or action from us, from the Federal

Government, on reimbursement. What are your thoughts on that today?

Mr. O'CONNOR. That I would like to keep the discussion going, sir.

Mr. BROWN. You would like to keep the discussion going.

What is your personal—if you had to make a recommendation to your—since you are making the decision, if you had to make the recommendation to your board of trustees today, would you recommend a specific amount that you reimburse the government, taxpayers, anything, that you reimburse the full amount?

Mr. O'CONNOR. Congressman Brown, I don't have a specific figure in my head at this point. That is why I would like to keep the conversation going, so that I can——

Mr. BROWN. Do you think you owe us something back in dollar amounts—not specific dollar amounts, but do you think you owe a dollar amount to us, back?

Mr. O'CONNOR. Congressman, I need to examine that very carefully, very carefully.

Mr. BROWN. You are in charge, right?

Mr. O'CONNOR. That is correct.

Mr. BROWN. Can you assure the subcommittee as a matter of policy that Pittsburgh will characterize and categorize all the costs associated with this situation as unallowable for Federal reimbursement?

Mr. O'CONNOR. Excuse me, I missed the beginning part of the question.

Mr. BROWN. Can you assure the subcommittee that as a matter of policy that Pittsburgh will characterize and categorize all its costs associated with this situation as unallowable for Federal reimbursement? In other words, the costs that you are bearing, you will—the law firms and whomever you may have retained or hired or expended moneys upon, that you will not ask any of that for Federal reimbursement?

Mr. O'CONNOR. That is correct, sir.

Mr. BROWN. OK. Does the University of Pittsburgh plan to reimburse the Federal Government for costs associated with generating significant amounts of unusable data? Putting aside the series of questions a moment ago, do you plan to reimburse the government for generating that data that was unusable? Should taxpayers pay for that?

Mr. O'CONNOR. We have not come to a conclusion on that yet, Congressman Brown.

Mr. BROWN. Again, back to the questions before, what is your thinking as the person in charge?

Mr. O'CONNOR. Sir, I think there are multiple costs involved; and if there are legitimate costs that we should reimburse, then the University's position is that it will reimburse.

Mr. BROWN. What are legitimate costs? Give me some examples of what you would consider legitimate costs that you should reimburse for.

Mr. O'CONNOR. I don't have one off the top of my head, Congressman.

Mr. BROWN. Give me costs that you shouldn't reimburse for.

Mr. O'CONNOR. That we should not reimburse——

Mr. BROWN. The government for. Since you can't come up with any costs that you should reimburse us for, are there any that you shouldn't reimburse us for?

Mr. O'CONNOR. There may be costs that the Federal Government should be reimbursed for, and as I said, the University will do that, but I don't have a compilation of those costs in front of me right now, sir. I will be happy to attempt to provide the committee with such.

Mr. BROWN. What is your role—what is your view, Dr. O'Connor, about the role of the University in overseeing NSABP with respect to the follow-up of the fraudulent activities of St. Luc in Montreal?

Mr. O'CONNOR. I think it is a very important role, Congressman, and I think we intend to take it very seriously, as Dr. Herberman has pointed out.

Mr. BROWN. Did the University take any steps to ensure that Dr. Fisher and his colleagues publish any reanalysis of the data in a timely manner?

Mr. O'CONNOR. We have requested that Dr. Fisher publish such materials.

Mr. BROWN. Prior to the public revelation of the fraud, did you ever take any steps to ensure that he published a reanalysis of the data?

Mr. O'CONNOR. Do you mind if I ask Dr. Detre some information on that?

Mr. DETRE. Congressman Brown, the University, sometime I believe in 1990, created a new office to investigate scientific integrity precisely because Mr. Dingell's committee has been critical of the quality of examinations we have done at the University. In that process—if you don't mind, I would like to describe the structure to you just in a sentence or two.

In this new office—it reports directly to the chancellor of the university via university counsel—the provost and the senior vice chancellor for health sciences are notified only when action has to be taken.

In the case of Dr. Poisson in Montreal, I have learned just a few weeks ago that our office notified the dean of the school of medicine that ORI has completed its investigation and instructed NSABP to do an analysis and publish the information. I was not notified about that, Congressman Brown, and maybe this degree of independence that the office currently has, which was set up for the protection of the university, has gone beyond its usefulness.

Mr. BROWN. Dr. Detre, in your prepared statement, you spoke about the culture of deference.

Mr. DETRE. Yes, sir.

Mr. BROWN. Culture of deference in academic settings toward a university senior scientist, something that obviously—I would think is not unique to the University of Pittsburgh certainly. Did that culture of deference at Pittsburgh toward Dr. Fisher, did that contribute to the university's failure of oversight?

Mr. DETRE. I believe it contributes to any university's failure because we don't have a mechanism in place to truly supervise senior faculty. Our expectation, Congressman Brown, is that if there are problems, they will be reported by the senior faculty member to the

chairman of the department and, through him, to the dean; but clearly, this mechanism alone is insufficient.

Mr. BROWN. You told the subcommittee staff in an informal survey that 90 percent of Pittsburgh's academic peers treat senior scientists in a sort of similar hands-off, detached fashion in a sense. Is this, in fact, a problem throughout the University?

Mr. DETRE. Congressman Brown, I think what I said to the distinguished staff of Mr. Dingell's committee is that every university has the same tradition of deference, that we are no exception to.

Mr. BROWN. In light of what has happened at your very fine university, what steps should the university take, or what steps do you plan to take, to grapple—to deal with this whole cultural deference to assure accountability and to be responsive to the public trust when Federal dollars or any government dollars are involved?

Mr. DETRE. Congressman Brown, as I earlier said to a question posed by Congressman Schaefer, I believe that an external quality assurance and auditing program is absolutely essential to guarantee the proper administration of these matters.

Mr. BROWN. Is the University of Pittsburgh going to lead the way?

This culture of deference that you have labeled clearly can cause potential problems in university settings across the country. Do you see any role for the University of Pittsburgh to serve to lead the way in beginning to undo some of that?

Mr. DETRE. We intend to be the leader in this, though I fully recognize, Congressman Brown, that it will not necessarily win a popularity contest.

Mr. BROWN. Talk to me a little about what "the culture of deference" means. I understand what it means exactly in this NSABP case, where there wasn't a challenge to things he was saying, but does it include things like these lavish conferences in Hilton Head and first class airfare and even—

Mr. DETRE. I don't think that has anything to do with it.

You know, as distasteful as it may appear to you, I don't believe that is the real problem. The real problem is that when deficiencies are identified—and I would like to remind you, Congressman, that actually it was NSABP that discovered the cheating at Montreal, not another agency; so the difficulties we find ourselves in—that we have no way of monitoring whether all necessary corrective actions have been taken or not. This is our major deficiency.

Mr. BROWN. Tell me some specific examples of some of the negative outgrowths of this cultural deference, how it is manifested in a way that does not add to public knowledge, might potentially abuse the public trust, is more of a negative than a positive.

Mr. DETRE. Congressman Brown, do you want to see an even more vivid example than what we are witnessing now, the reason why we are here?

Mr. BROWN. Sure.

Mr. DETRE. I think it is a perfect example of the difficulties universities find themselves in, because we do not have a university-based but independent quality assurance and audit program which would help us to identify problems and correct them.

Mr. BROWN. Why not?

Mr. DETRE. It has not been part of our culture, Congressman. The society learns gradually from its mistakes.

I remember that 15 years ago neither Congress nor universities had any conflict-of-interest policies. We now have them. I think this is a gradual growing process. We learn from our mistakes, and we try to rectify them.

Mr. BROWN. Dr. O'Connor, I assume you are going to accelerate some of that learning process?

Mr. O'CONNOR. I certainly hope to, Congressman Brown.

Mr. BROWN. Thank you, gentlemen, for testifying, for being with us today. We will take a short, 15-minute recess or so, while the chairman and the rest of us vote. Then we will call Dr. Fisher immediately upon returning.

[Brief recess.]

Mr. DINGELL. The Chair advises the next panel is composed of Dr. Bernard Fisher, M.D., former chairman, National Surgical Adjuvant Breast and Bowel Project.

Dr. Fisher, welcome to the committee.

The Chair advises that all witnesses are sworn before the committee. Do you have any objection to being sworn in?

Mr. FISHER. No, sir.

Mr. DINGELL. Very well. The Chair advises that you are, since you will be testifying under oath, entitled to be advised by counsel. Do you so desire?

Mr. FISHER. Yes, sir.

Mr. DINGELL. Your counsel is seated next to you. You are?

Mr. ONEK. Mr. Joseph Onek, Mr. Chairman.

Mr. DINGELL. How do you do, sir. The Chair will note for the record that you will then be advising Dr. Fisher. The Chair advises that copies of the rules of the subcommittee, the committee, and the House are there at the witness table to assist you as you testify before the committee.

If you have, then, Doctor, no objection to testifying under oath, if you will please rise and raise your right hand.

[Witness sworn.]

Mr. DINGELL. You may consider yourself then under oath, Doctor, and the Chair will recognize you for such opening statement as you choose to give.

TESTIMONY OF BERNARD FISHER, FORMER CHAIRMAN, NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT, UNIVERSITY OF PITTSBURGH, ACCOMPANIED BY JOSEPH ONEK, COUNSEL

Mr. FISHER. Thank you, sir. Mr. Chairman, members of the subcommittee, I am grateful to have the opportunity to be here today. I am Dr. Bernard Fisher, distinguished service professor of surgery at the University of Pittsburgh. Over the years, I have been a member of the President's Cancer Panel, the Board of Scientific Counselors, and the National Cancer Advisory Board of the National Cancer Institute.

I have passionately devoted more than 35 years to the study and treatment of breast cancer to the exclusion of almost everything else in my life. My studies involving nearly 50,000 women and

5,000 health professionals at 500 institutions in North America have, I believe, revolutionized the treatment of that dread disease.

As a result of the research by the NSABP, which I chaired for 27 years, women with breast cancer now have a choice to save their breasts rather than to undergo a disfiguring radical mastectomy. Our work has shown that chemotherapy and tamoxifen after surgery increases survival.

We recently began the study to determine whether breast cancer can be prevented in women at high risk. If the findings from that trial indicate that the risk of breast cancer can be reduced, the problem of breast cancer would be significantly diminished.

The events arising out of the data falsification in Canada have been tragic for me, my colleagues, our families, and for all women in this country. Women with breast cancer began to doubt the therapy they had received. Those without breast cancer lost confidence in the system that they someday might need to rely upon.

Mr. Chairman, I can't emphatically enough state that women must not become the victims of these events. In my statement, I will address point by point specific matters that have arisen during the past few months.

First, I sincerely share the subcommittee's concern regarding fraud in science and believe that any deviation from scientific integrity is not acceptable. My whole scientific life has been based on that credo. I deeply regret that there was data falsification by a physician at one of the hospitals participating in the NSABP.

Second, despite the data falsification, women can and must feel secure that lumpectomy following radiation therapy is as effective a treatment as removal of the breast. Our studies, as well as those of others, have consistently supported our findings. The NCI, upon recent review of our results, reached the same conclusion.

Third, there never was any intent to hide information regarding the discovery of falsified data at St. Luc Hospital in Montreal, and I emphasize that. There never was any intent by me or my associates to hide any information regarding the discovery of that information.

On November 14, 1990, I was notified by Dr. Carol Redmond, Director of the NSABP Biostatistical Center, that data discrepancies found at St. Luc Hospital were being investigated. At that point, no fraud had been identified.

In February 1991, following further investigation by the Biostatistical Center, it was found that data falsification had occurred. We immediately notified the NCI and the investigator, Dr. Roger Poisson, was suspended.

We believe that the detection and reporting of the St. Luc Hospital fraud was carried out according to the 1988 clinical trials cooperative group program guidelines which state that, "In more serious cases, it is the responsibility of each group to define the gravity and degree of potential problems and to be consistent and fair in the actions and sanctions it applies when significant problems are uncovered." The time spent by the NSABP investigation was used to ensure that a fair action was taken.

After we alerted NIH, an official investigation was begun by the Office of Scientific Integrity, OSI. We were embargoed from further discussions of the matter. On several occasions, the data from

NSABP studies in which Dr. Poisson participated were reanalyzed, eliminating his patients.

In March of 1992, the findings were shared with members of the NCI, OSI, and NIH. These findings indicated that when all data from St. Luc Hospital were removed from the reanalyses, the outcomes and conclusions of all of our previously published studies were unchanged. We had already notified the NSABP Executive Committee of the Poisson affair and of the results of our reanalyses in February of 1992.

The OSI thorough investigation found falsification in 99 breast cancer patients in 22 studies. These falsifications represented 0.3 percent of the 33,885 women in our studies; 98 of the 99 alterations were related to patient entry criteria. In randomized studies, such types of falsifications are unlikely to influence patient outcome.

Let me emphasize this firmly, if our reanalyses had produced evidence that the conclusions of our studies were affected by the data alterations, we would have reported our findings immediately. Neither we, the NCI, the NIH, nor the OSI perceived that the Poisson falsifications had resulted in a public health problem. If the NCI had considered this to be the case, they could have issued a clinical alert.

Our plan was to present our findings to the scientific community in a peer-reviewed publication and to prepare a comprehensive technical report. We didn't realize that the failure to publish our findings immediately would be misinterpreted by the public as an indication that we were concealing information. Such a perception resulted in the unjustified concern that women with breast cancer were receiving inappropriate therapy.

We should have been more sensitive to this possibility and we should have published our reanalyses more promptly, and I truly apologize for that delay.

For 30 years, the goal of the NSABP was to provide better information to patients and their physicians. The suggestion that we suppressed information is painful. We never attempted to hide any information. There could have been no conceivable reason for us to do so.

Fourth, concern has been raised regarding inclusion of data from St. Luc Hospital in NSABP reports published after February 1991, when the Poisson fraud was found. There are honest differences of opinion among statisticians regarding the handling of falsified data in large clinical trials. There are significant scientific reasons not to exclude all such data.

Our statisticians considered that it was not appropriate to exclude all data from those patients who had a diagnosis of breast cancer and who had been randomized, treated, and followed appropriately. Excluding all patients would have prevented identification of toxicities and other adverse events.

During the OSI embargo, we could not exclude data without discussing the findings with journals; and after the embargo was lifted, we complied with the NCI request of January 1993 that no data from St. Luc be included in publications containing new data.

A fifth concern relates to the reporting of deaths from endometrial cancer in breast cancer patients treated with tamoxifen. As was mentioned previously, there are more than 4

million women using that drug. Clinical trials have demonstrated that the benefit from tamoxifen is about 20 times greater than the risk of getting endometrial cancer. Consequently, women with breast cancer should continue to take tamoxifen, although some undesirable effects may occur.

In our studies, we found that of 2,693 breast cancer patients being treated with tamoxifen, 23 developed endometrial cancer and 4 deaths occurred. There is no substance to the suggestion that we withheld information concerning these four deaths.

It is important to understand the difficulties involved in determining the cause of death in breast cancer patients with endometrial cancer. When a death occurs in a woman who had both breast cancer and endometrial cancer, it is extremely difficult to be sure which cancer caused the death. It cannot be assumed that the death occurred as a result of the endometrial cancer; she may have died of breast cancer. Only by continuing medical review and rereview and by obtaining difficult-to-get information can we be sure which cancer caused the death. Such medical detective work can take a long time.

There is often delay in obtaining information about deaths because patients move, go to different hospitals, change physicians or because families fail to notify physicians about a death. These delayed responses can result in a delay in confirming the cause of death. Death certificates can be ambiguous or inaccurate and not readily obtainable. Autopsies are infrequently performed and often fail to aid in determining the cause of death.

In the fall of 1993, we confirmed that there had been deaths from endometrial cancer in tamoxifen patients and reported this fact to the NSABP, the NCI, and the drug manufacturer. In retrospect, it might have been possible to collect and report information about these deaths sooner, but there was never any intent to withhold any information.

Sixth, concerns have been raised about the NSABP audit procedures. The NSABP verifies and evaluates the quality of data submitted by a quality assurance program which has two parts. One is the on-site audit program in which visits to participating institutions are made at least once during a 3-year period by NSABP personnel. Selected samples of patient records are examined.

In the second part of the program, extensive source records from all patients are received and examined at the NSABP headquarters. In 1991, the reviewers of our grant application to the NCI termed our procedures "exemplary."

Since 1991, there have been significant changes in the workload of the NSABP. The initiation of the breast cancer prevention trial has resulted in an increase in the number of patients being followed in NSABP studies from 25,000 in 1991 to 41,000 in 1993; and the number of data forms processed expanded from 225,000 in 1991 to 413,000 in 1993.

In retrospect, the administrative infrastructure of the NSABP did not keep pace with this tremendous growth. There have been some delays in our auditing and reporting functions.

I accept my share of the responsibility for these administrative deficiencies that occurred; I could have been more aggressive in seeking funding for additional administrative personnel. In retro-

spect, I should have brought on more executive administrative people to help manage the program, an executive director. Perhaps my passionate attention to the science overshadowed my administrative insight, and this was a mistake. I should have been firmer with the personnel responsible for the audit program.

I believe that the administrative deficiencies of the NSABP could be remedied quickly. For this reason, I am troubled by the prolonged suspension by the NCI of all NSABP clinical trials in progress and the postponement of the development and start of new studies. These events could affect the lives of thousands of breast cancer patients in years to come. Clinical trials must be restored at once.

Women and their doctors must realize that large multicenter randomized trials are the best way to obtain information for making treatment decisions. The randomization of patients in trials eliminates the chance of obtaining biased results.

Clinical trials also provide—and I emphasize this—higher standards of patient care. If clinical trials are eliminated, we have no good alternatives. We cannot return to the system where treatment is based on physicians' intuition.

Finally, I thank the NCI for the support which made my life's work possible. For 25 years, NSABP's relationship with officials of the NCI was based upon mutual respect and cooperation. Members of the NCI have been involved in every aspect of our efforts. They have continuously been aware of and have participated in our successes and were intimately involved with the decision-making process of our group. This was truly a cooperative agreement in name and in fact.

It is necessary for the good of the women in this country that we now look to the future. Within the last 6 months, I have formulated a strategic plan for a new generation of clinical trials, which I hoped would be my legacy, which could significantly alter the future treatment of breast cancer patients.

One such study evaluates the use of preoperative therapy, and if the results indicate, primary surgical treatment for breast cancer will become obsolete. Information from another study could more clearly define a patient's risk for developing a treatment failure and consequently identify which patients should or should not receive a particular therapy. Other studies by us are evaluating new and exciting therapeutic agents that can be better than those currently used.

For progress to be made in breast cancer treatment, the public's faith in clinical trials must not be diminished by these current events or any other.

In conclusion, I emphasize that any deviation from scientific integrity is unacceptable. While fraudulent data were submitted by a contributing investigator, the NSABP studies themselves are not fraudulent. There was never any intent to hide information or deceive anybody. During the course of all our activities, NCI and Zeneca were intimately involved.

System errors can and did occur and must be repaired. I believe, as was heard, improved technology will help. Above all, we must not allow these recent events to deflect us from our ultimate goal—the prevention and cure of breast cancer in women.

Thank you, sir.

Mr. DINGELL. Thank you, Dr. Fisher. The Chair is going to recognize himself first.

Doctor, could you tell the subcommittee the importance of an audit program to a clinical trial such as the one you headed at NSABP, please?

Mr. FISHER. Yes, sir. The purpose of an audit program is to verify the quality of information that is being obtained and is being submitted to the NSABP Headquarters.

Mr. DINGELL. Now, Dr. Fisher, during the course of the trials conducted at NSABP, your staff conducted literally hundreds of these audits; is that correct?

Mr. FISHER. Yes, sir. There were 587 audits conducted in four cycles.

Mr. DINGELL. Now, Doctor, tell me who is Dr. Wickersham or Wickerham?

Mr. FISHER. Dr. Wickerham is the Deputy Director of the Operations Office.

Mr. DINGELL. He is the chief medical person in the study, is that right, and the auditors reported to him?

Mr. FISHER. The audit program has two parts. The audit program has a part which is conducted by the Biostatistical Center. The Biostatistical Center is the one responsible for scheduling audits, sending out people to audit the program, to bring and to examine the things that they do at the site, and to bring back to the Headquarters source information, reports of x rays, all kinds of things, laboratory information, information about treatment, and so on; and then at the Headquarters, by the Biostatistical Center, this is all reviewed to make sure that what was sent in originally is that which exists in the source document.

Mr. DINGELL. Dr. Wickerham told the subcommittee staff that he routinely gave you copies of the audit reports at the NSABP sites; is that correct?

Mr. FISHER. I received audit reports. I cannot say with certainty whether these were routine or all audit reports, but I did receive audit reports.

Mr. DINGELL. Now, Doctor, the subcommittee staff has been reviewing the audit reports for the last month or so, and it has found that in addition to the St. Luc problems relative to fraud, your auditors uncovered a number of similar problems at sites throughout the NSABP.

For example, a number of locations were found to be violating the eligibility criteria. At one site, ¾ of the patients enrolled did not meet the eligibility criteria. Can you tell us about what you knew about these matters regarding the depth and the breadth of eligibility problems identified by your auditors?

Mr. FISHER. Mr. Chairman, we recognized that there were administrative deficiencies in the audit program, but with respect to any particular institution, we have not had a chance to review the subcommittee's investigations or reports or any other recent analyses, and we would certainly like to have the opportunity to do so and provide the information to you. There may be some misunderstandings regarding clarification of ineligibility and other terms which exist.

Mr. DINGELL. I am not going to refer to the specific sites unless it appears to be desirable so to do, but these were audits which were performed over the years, clear back into the 1990's, the early 1990's, and on back even beyond that into the 1980's. And that was at a time when you were in charge of the program, and didn't they give you some awareness of the fact that there were problems with either fraud or slovenly work?

Mr. FISHER. Well, it was the audit process which did uncover the St. Luc; it was the part of the quality assurance program which uncovered the St. Luc falsifications. We found those falsifications through our efforts, and reported them, and that is the only falsification that has been——

Mr. DINGELL. Of course, Doctor, these went to eligibility and showed that there were some fairly significant eligibility questions. For example, one site had three-quarters of the participants ineligible.

Mr. FISHER. I am certainly unaware of that, sir. I really am not aware of it.

Mr. DINGELL. But it was in audit reports that came to you, though.

Mr. FISHER. I don't, I really don't remember seeing that report at all.

Mr. DINGELL. Well, here they are, and I am just going to lay them out. South Nasau Hospital, Rush Presbyterian Hospital, St. Joseph Hospital in Lancaster, and in the University of Pittsburgh. Now, the University of California Davis had ¾ of the participants in the study ineligible.

Mr. FISHER. I have never seen that.

Mr. DINGELL. These were audits, these were your audits in your project.

Mr. FISHER. May I make a comment about eligibility?

Mr. DINGELL. Sure.

Mr. FISHER. Eligibility has been—the term "eligibility" has been used here and elsewhere. Eligibility is not falsification.

Mr. DINGELL. We are not—I am not making the allegation that eligibility is a fraud, or fraud or similar question. It is, however, a matter which goes to the very reality and scientific adequacy of the test, because if you are testing people or reporting on people who don't meet your eligibility requirements, it tends to skew your results. And what I am trying to find out is, all of these matters were essentially found in audits, but we are not able to address them here today because of your lack of familiarity with them.

Mr. FISHER. I certainly am not aware of any institution where there were ¾ of the patients ineligible. I should like to have more information about that than I have.

Mr. DINGELL. Well, we will give it to you. It is, however, I would observe, Doctor, in your own audit reports.

Now, here are other examples. Auditors turned up instances where patients were randomized twice. What is the result of randomizing a patient twice in a study of this kind? What does it do to the statistical validity of the study?

Mr. FISHER. I can't answer that question.

Mr. DINGELL. Do you know how much double randomization was occurring and what the practical effect of it was?

Mr. FISHER. Sir, I don't know the number of double randomizations, but I must think they were extremely few and far between. This has not been brought to my attention as being a problem.

Mr. DINGELL. Well, your auditors also identified a number of informed consent problems throughout the site—throughout the different sites. For example, no documentation of informed consent obtained up to 2 years—obtained up to 2 years post randomization and so forth. Now, what—first of all, does this constitute a problem in terms of lack of adequate informed consent by the participants, and if so, what was done?

Mr. FISHER. Let me say emphatically that informed consent is a very important part of what we are doing. It always has been.

Mr. DINGELL. It is really an ethical question.

Mr. FISHER. Absolutely. There is no question about that. And as far as I am concerned, that is something that there can be no excuses for. There are certain situations where in one of the studies, for example, wherein formed consent may have been obtained after an operation was done that is in a particular study of lumpectomy where prerandomization was used, but in reference to your comments about informed consent, I have seen in some of the audit reports that there was this kind of situation, but I have not been familiar with it as any kind of a serious problem.

Mr. DINGELL. Well, your auditors found a number of sites that were not maintaining drug laws. Can you tell us the importance of the drug laws—rather the drug logs and what happened at the locations that were not properly maintaining these logs?

Mr. FISHER. Drug logs are also something that is looked for at the site routinely to make sure that the drugs that are given to the investigators are used for the patients that they are supposed to be used on.

Mr. DINGELL. Well, but here you have another instance where the drug logs were not maintained. Is that important, or is that not important?

Mr. FISHER. As far as I am concerned, it is important.

Mr. DINGELL. Now, a number of other locations had serious problems with missing data. Were you aware of this?

Mr. FISHER. I have heard about that, particularly in certain institutions, and it depends again on how long ago the data was collected. For example, at one of the—in New Orleans, for example, where data was collected in the 1970's at a large city hospital, some of that data now in 1994 may be hard to obtain. I cannot know more than that about it, however.

Mr. DINGELL. Well, if the failure to maintain proper logs and to have the data properly assembled is recent, is that a more serious problem?

Mr. FISHER. These things are all problems. There is no question about that. And I would certainly like to address them after I knew more about the degree of these problems. For example, I indicated to you that the NSABP had conducted 587 audits since 1982, and of those 587 audits, there were only—there were major problems identified in 5.8 percent, and some of those problems deal with the things that you are talking about.

Mr. DINGELL. You mean there were problems identified in 5.8 percent of the audits?

Mr. FISHER. Which were considered to be serious enough to suspend these investigators.

Mr. DINGELL. Well, these involved some 30 institutions. Are you able to tell me that these were trivial matters or that they were not important matters?

Mr. FISHER. No, sir. I in no way make any indication that these are trivial. We do the audits to determine these things. Otherwise, there would be no point in doing the audit program.

Mr. DINGELL. Well, I think you raise an important question. What did you do with the audits? The audits come in, they said, for example, there is a problem with informed consent. They say that a number of sites were not maintaining drug logs. They say that there was a serious problem with missing data. Did you inquire into these problems?

Mr. FISHER. The usual process would be that when this happens, the medical auditor, medical reviewer, will write a report, and that report will indicate to the investigator what the problems are and we would expect them to implement a plan of action to tell us what they are going to do to correct these problems. And then all this—this report also goes to a quality assurance committee which we have.

We have a standing committee where all of these reports go to their review and their suggestions as to what kind of punitive action should be taken. The investigator is notified about these; he is—he or she is supposed to provide the NSABP with a plan of action that will be acceptable, and if it is acceptable, then the decision is made to give them a chance to show that they have corrected themselves and resume accrual. If it is not acceptable, accrual continues to be suspended.

Mr. DINGELL. Well, that is all very good. Were you ever made aware of the fact that there were problems with informed consent? Were you ever made aware of the fact that there were problems with sites not maintaining drug logs? Were you ever made aware of the fact that a number of locations had problems with missing data?

Mr. FISHER. As I said, I have seen these reports sent to me by Dr. Wickerham. At this moment I don't know what was in the reports, how many of them were related to informed consent, how many of them were related to drug log problems. I am unable to answer that, sir.

Mr. DINGELL. Well, you are able to tell us what was done about these matters. What was done about the informed consent question? What was done about the questions on the number of sites that were not maintaining drug logs? What was done about the sites where there were problems with missing data? What action did you take?

Mr. FISHER. Well, we sent the reports back. One of the purposes of an audit program, aside from what I mentioned, is also that it is supposed to be and is a program, an interactive program where investigators are informed about their deficiencies and are educated against doing—repeating this.

Mr. DINGELL. What did you do about these matters to correct the situation, either in general or in any particular case? Did you do anything? Can you tell us any one thing you did on any one of these audits which came to your attention? Did you do anything about any of the audits which came to your attention with regard to either the questions of informed consent, questions of inadequate drug logs, or failure to maintain drug logs, and also locations that had problems with missing data? Can you tell us anything you did about any one of the audits on any one of these points?

Mr. FISHER. I certainly—my main issue here would have been to order the personnel who were responsible for this program to carry out what they were supposed to do.

Mr. DINGELL. Well, what were you doing while these people were supposed to do these things?

Mr. FISHER. I think what we were doing, sir, is that the NSABP did have continuing, ongoing workshops, meetings for data managers, for all kinds of people to educate them into—to try to get them to prevent this kind of practice. This was what was being done.

Mr. DINGELL. What was your job at NSABP?

Mr. FISHER. My main role in the NSABP, and I take—but let me emphasize that I take full share of responsibility—full responsibility for the administrative errors which took place under my term, but I was, as I mentioned in my introductory statement, my main interest was to be—to try to do the best science that would be possible, which would affect the most women in the world with breast cancer. I was on top of the development of the scientific program, the implementation of the scientific program, the pooling together of the information and the publication of the science, and these were the chief efforts that I conducted.

Mr. DINGELL. Well, let's look. What was your job at the NSABP?

Mr. FISHER. As I say——

Mr. DINGELL. You were the head of the whole operation, were you not?

Mr. FISHER. Yes, sir.

Mr. DINGELL. And you got these audit reports?

Mr. FISHER. I take responsibility for the operation; I wasn't the head of all of the pieces that were under me. The biostatistical center, the data center which is a major part of the NSABP; it actually receives more of the funding than does the operations center.

Mr. DINGELL. Who was responsible for management and administration?

Mr. FISHER. The management and administration was delegated in certain areas. The fiscal administration——

Mr. DINGELL. To who?

Mr. FISHER [continuing]. —Was given to a fiscal officer who had been with me for 20 years who had a staff of people that conduct all of the fiscal affairs in concert with the University of Pittsburgh fiscal office. All of that was integrated.

Mr. DINGELL. What did this individual do with the audits? Did he do anything with them?

Mr. FISHER. At one time Ms. Dash, who was the—was the fiscal officer, her job was to—all of the audit reports came to her before

they were finally sent out, and it was her job to see that they did get distributed.

Mr. DINGELL. Did this person report to you?

Mr. FISHER. She always reported to me as——

Mr. DINGELL. She was responsible to you, was she not?

Mr. FISHER. Yes, sir.

Mr. DINGELL. And you were responsible for her; is that right?

Mr. FISHER. Yes, sir.

Mr. DINGELL. Now, the chief auditor, Marjorie McLaughlin, told the subcommittee staff there were a number of chronically problematic sites, such as Tulane and LSU. Were there any special efforts taken to try to deal with the sites that seemed to come up year after year to exhibit an inability to follow the protocols of the study?

Mr. FISHER. Yes, sir. In talking with the principal investigator on many occasions by myself and by our staff, there was a Catch-22 in that situation.

Mr. DINGELL. What was the Catch-22, Doctor?

Mr. FISHER. Well, the Catch-22 was simply this, and this has been a part that we had experienced over many years. The institutions that put on the larger numbers of patients who did put on large numbers of patients, if they had problems and if those institutions were to be eliminated from the NSABP, the backlog, the large numbers of patients that needed to be followed up still remained there to be followed up. And so we did keep those people, when we suspended them, we kept them on for at least follow up, until——

Mr. DINGELL. Well, I have no quarrel with follow up; I will concede that this is very important. But that would be a part of the research protocols in any event, that they had to follow up; would it not? If only to assure the health and the safety and the well-being of the patient.

Mr. FISHER. Absolutely.

Mr. DINGELL. All right. So they had that responsibility, whether they remained in the test program or not. But was there ever any disciplinary action taken against Tulane or LSU or any of the others which were either chronic problem areas or which failed to deal properly with the problem of informed consent, or which failed to keep proper drug logs, or which had serious problems with missing data?

Now, we have established that you had all of these difficulties, and I am trying to find out what one thing that you did with regard to any of the sites which were deficient, some of which, as we have indicated, were chronically problem sites and others of which had significant failures.

Now, what one thing did you do or what one thing did anybody else do about these sites which were problems?

Mr. FISHER. We suspended their accrual and gave them——

Mr. DINGELL. When did you do that? How many of them did you do that to?

Mr. FISHER. How many of them did we do that to? In the last cycle 4 in which we did 154 audits—129 audits; I think there were 6 that were suspended.

Mr. DINGELL. But they were suspended, and for how long were they suspended?

Mr. FISHER. As I recall, for varying periods of time, depending upon what the problem was, how rapidly they could get it corrected. I can't—I don't——

Mr. DINGELL. Who were the six that were suspended?

Mr. FISHER. I don't have that at my fingertips.

Mr. DINGELL. Were Tulane or LSU suspended?

Mr. FISHER. Not in the last cycle, no. Earlier, but not in the last cycle.

Mr. DINGELL. But your auditors tell us they were chronic problems. Now, what did suspension mean? Did suspension mean that they were removed from the test, they were removed from the test until they had corrected the problems?

Mr. FISHER. They were unable to put any more patients on to the studies until those problems were corrected. We hoped to keep them there, to keep the patients followed that were there, and that was it.

Mr. DINGELL. But they continued to participate with the patients that they had on in the program; is that right?

Mr. FISHER. They continued, they continued, but didn't have any activity, other than what you say.

Mr. DINGELL. OK. So they are continuing to submit data.

Now, have you suspended, let's say, institution X for bad data and missing data? You kept them on to continue with their efforts and to continue supplying missing data?

Mr. FISHER. No. We certainly did not. We tried to provide them with——

Mr. DINGELL. Well, you told us you had kept them on and you kept them on. You didn't allow them to enroll new patients, but you kept them on. So you kept them on and they continued the same practices. They continued the same practices with regard to failure to achieve proper informed consent, failure to maintain proper drug logs, and failure to provide adequate data.

What I am trying to find out is what disciplines did you have, what did you do, how did you—how were you able to tell us when your own chief auditor tells us that there were a number of chronically problematic sites, and I am asking you what did you do about any one of these to see to it that they corrected their bad practices? What did you do about to see that they corrected their bad practices? You suspended them, but they continued apparently according to your chief investigator, providing bad information, and engaging in other practices which, quite frankly, raise questions about the value and the integrity of the scientific process involved in this particular study.

Mr. FISHER. Sir, I cannot answer these questions unless I know the specific cases and so on. I am sorry. We continue to try to educate these people.

Mr. DINGELL. It is my impression that you were the man that ran this whole thing.

Mr. FISHER. The—in terms of our involvement with these principal investigators, we did talk to them; we did try to educate their data managers; we did try to have affirmative kinds of things in that nature.

Mr. DINGELL. But your auditors continued to find chronic problems.

Mr. FISHER. I don't know.

Mr. DINGELL. Didn't they tell you, we have a problem here, and didn't you in looking at the audit say, by golly, we saw them last week or last month or last year and we saw them the month before that and the year before that and the month before that and the year before that? Were you paying any heed at all to these matters, Doctor, or were you delegating it to somebody who was not reporting to you, or were they reporting to you and you not paying heed to them?

Apparently the auditors sent you reports with which you do little or nothing, and apparently the chief auditor tells us about a number of chronic problems sites. And apparently the people whom you delegated to deal with the administrative end of the business didn't deal with the administrative end of the business in terms of bringing it to your attention, or if they did, you didn't pay heed to it because the situation went on over the entirety of the years. What can you tell us about this?

Mr. FISHER. I can tell you that I accept responsibility for any inadequacies that took place, and I am very sorry for that, and——

Mr. DINGELL. Here is another question. Let's take Memorial Cancer Research Foundation, Dr. David Plotkin. They were identified by NSABP auditors in a report in 1990, and a transmittal letter with findings was to be shipped to Dr. Plotkin and to NCI. The signed letter and the envelope sat in NSABP files until recently and the audit report never left the NSABP. How did this happen?

Mr. FISHER. I did not know about this until others knew about it.

Mr. DINGELL. Well, let's assume that it is true, and I believe that it is. You never notified the people about their failures. The audit report never left the NSABP.

Mr. FISHER. I don't know, sir. It may not have or it may have.

Mr. DINGELL. I am going to—I have to go to the Floor; I am going to ask Mr. Brown to continue presiding. I will be back just as quickly as I can.

Mr. Brown, would you take the chair please, sir.

Mr. BROWN [presiding]. I thank the chairman. The gentleman from Colorado, Mr. Schaefer.

Mr. SCHAEFER. Thank you, Mr. Chairman.

Dr. Fisher, after the media broke the story on the data falsification by Dr. Poisson, you purportedly reanalyzed the data and briefed ORI. Dr. Bivens told us in April that your presentation was oral and was not written; is that correct?

Mr. FISHER. Presentation to the ORI, the NCI, NIH people was presented orally in 19—March 1992 at their request. There had been many reanalyses done by the five statistical centers of the NSABP, Dr. Redmond and her associates. She did one almost immediately following the finding of the first—the proof of falsifications. She did another one which was presented at this meeting that you are referring to. There were others that were done subsequently and at one point material of a reanalysis was submitted to the NCI. So that there were repeated reanalyses.

And at the time of the one at the—one that was presented to the ORI, it is my recollection that there was total acceptance of this audit—of this reanalysis, and there were no comments either spoken or written to us regarding any concerns about the reanalysis.

Mr. SCHAEFER. Well, so it was oral. And is this the common practice not to do this in writing?

Mr. FISHER. It is what we were asked to do, sir.

Mr. SCHAEFER. Asked to do by——

Mr. FISHER. Asked to do by the ORI.

Mr. SCHAEFER. By ORI?

Mr. FISHER. Yes, sir.

Mr. SCHAEFER. All right. Now, was this a complete reanalysis?

Mr. FISHER. Yes, sir. Complete reanalysis of all protocols which Dr. Poisson had submitted patients to.

Mr. SCHAEFER. Was this a running update, though, over a period of time where you kind of looked at new things all the time?

Mr. FISHER. No, sir. No. It was a complete update at one time, one point in time.

Mr. SCHAEFER. All right. At the hearing we had in April, we were told that it was not a complete reanalysis.

Mr. FISHER. To the best of my knowledge, sir, and the best of my remembrance, it was——

Mr. SCHAEFER. And it has been done since then?

Mr. FISHER. It has been done since then many times, yes.

Mr. SCHAEFER. Yes, but since April?

Mr. FISHER. It has been done since April, yes. I am terribly sorry that Dr. Redmond isn't here, because Dr. Redmond, who is the statistician who is in charge of all of this, would better address these issues than I can.

Mr. SCHAEFER. Well, again, as the chairman spoke, you were in charge of this whole thing?

Mr. FISHER. Absolutely.

Mr. SCHAEFER. So therefore, you know, sooner or later the buck stops somewhere.

Mr. FISHER. Right, sir.

Mr. SCHAEFER. This Dr. Poisson, what is he doing these days?

Mr. FISHER. I haven't the vaguest idea.

Mr. SCHAEFER. After you were made aware of the fraud that had been perpetrate by Dr. Poisson, you stated that you immediately notified NCI. Tell me, did you ever notify the editors of the New England Journal of Medicine or any other publications about this so that some of your colleagues would know what was going on?

Mr. FISHER. No, sir, because at that point in time we were embargoed by the ORI, for during their entire investigation, we were only permitted to present—to tell people about this under a need to know, and there was no—so to answer your question, no, we did not.

Mr. SCHAEFER. Now, you say you were embargoed, but you still provided this to NCI, this information?

Mr. FISHER. I am sorry.

Mr. SCHAEFER. You say you were embargoed, but you still—you provided the information on the fraudulent findings to the NCI?

Mr. FISHER. Well, that was certainly a need to know.

Mr. SCHAEFER. But that was as far as it went, then?

Mr. FISHER. Yes, sir. We did get one—we requested from the ORI that we be permitted to report this to our NSABP executive committee so that they knew what was—that this was an affair that was going on.

Mr. SCHAEFER. What was the answer?

Mr. FISHER. And we did give it to them, to the executive committee. In February of 1992, we presented the fact that this was going on and we also presented them with one—with the reanalysis to indicate to them that taking all of the data out in all of these reanalyses failed to influence the outcome—either the outcomes or conclusions of any of our studies that had been previously reported.

Mr. SCHAEFER. So therefore, now the embargo is lifted?

Mr. FISHER. Yes, sir.

Mr. SCHAEFER. OK. Then did you inform the New England Journal of Medicine or any other publication of this, and if not, why not?

Mr. FISHER. I guess the most direct answer to your question is that why we did not immediately or otherwise inform them is because we really didn't know that this was necessary to do.

Mr. SCHAEFER. Even though you knew there was fraud there?

Mr. FISHER. The point is that doing all of these reanalyses did not in any way alter the outcomes or conclusions of our studies. There was no alteration whatsoever, and so therefore, that is——

Mr. SCHAEFER. All right. Let me get this straight, then. So, no, you did not inform any medical journals of this falsified data?

Mr. FISHER. I am sorry.

Mr. SCHAEFER. You did not inform any medical journals of this data after the embargo was lifted?

Mr. FISHER. At that time, right.

Mr. SCHAEFER. You did not.

Mr. FISHER. Right.

Mr. SCHAEFER. I have a little bit of trouble figuring out why you wouldn't when we have all of these women throughout the country who are looking at these procedures or possible procedures trying to figure out which way they should go and we have doctors all over the place that would, I would think, dearly love to have this information.

Mr. FISHER. Well, as I have said, there was no evidence in any way that these data had been changed, that the outcomes had been changed, and therefore, we did not really perceive this as a major problem, public health problem or otherwise, and again, as I said in my remarks, had I been circumspect enough to think that in March of 1994 this would have become the problem that it has, certainly we would have been more interested in doing so.

But let me also say that we did have a plan of action as to what we were going to do, and that plan of action was to present a full report in a peer review journal with a technical report because there is so much data that, so much information that one single report—one single paper could not hold it.

The strategy of the biostatistical center, biostatisticians was to do that, have a full technical report available to everybody and have a paper which would indicate what the findings were.

Mr. SCHAEFER. If they asked for it.

Mr. FISHER. To publish the paper, publish the paper in a journal, but a technical report on file.

Mr. SCHAEFER. Now, let me also get this straight. You are saying that the fraud did not change results of the study; is this correct?

Mr. FISHER. Yes, sir.

Mr. SCHAEFER. I have a tough time figuring this one out. I am obviously not a medical doctor, but it seems to me if there was fraud and there was falsification of information, how could it not—how could it not?

Mr. FISHER. Well, I think you raise a very important question and what you are asking is a very, very important one. And it gets into the problem of what do you do with the kind of data that were obtained, oh, falsified data or even ineligibility patients and all of that sort of thing.

Now, there is a—the biostatistical community, the biostatisticians have a—their feeling about this, their belief, their—most of the major statisticians, Professor Pita from Oxford, who is one of the leading statisticians in the world, et cetera, et cetera, feel that—you have several choices when you are faced with information like this. You can either take all of the data out in doing your reanalysis, just throw it all away, or you can only take out that which was the flawed data. In other words, in the lumpectomy study of these thousands of patients, there were only six where it was demonstrated that there was truly fraudulent data. And you can get rid of those.

So you can take them all out, take out just those that are fraudulent, or you can leave them all in. And this is known as the intent-to-treat principle. And that is—so that is a consideration.

And the statisticians in the NSABP reached their own conclusion that they felt, and that was one of the things after the April—during the entire process, their intent was to use the intent-to-treat principle.

Mr. SCHAEFER. All right. If we leave this information in, the fraudulent information in, do you not feel that the American public has a right to know?

Mr. FISHER. We didn't leave it in, we took it out. We took it all out.

Mr. SCHAEFER. Well, regardless, it just seems to me that women out there should know whether a study, conducted with American taxpayers money included fraudulent information. This was not divulged. That is what I don't understand and what the chairman doesn't understand and this whole committee doesn't understand. Why wasn't this divulged?

Mr. FISHER. We had a plan for divulging it in a rational, regular basis.

Mr. SCHAEFER. Yes. But that was after a number of women in this country had this surgery already.

Mr. FISHER. Nothing from our findings indicated that they had any improper therapy.

Mr. SCHAEFER. I guess—and I know my time is up and I will be back for some more questions, but it just seems to me for them to make an important decision like this on whether they go with lumpectomy or mastectomy, they have to have every possible shred of information that is out there. If there is fraudulent data in

there, they should be there for them to make this decision. Maybe only six of them turned up problems or whatever it is—this has to weigh heavily on whatever the final analysis is by this individual woman. That is what really concerns me.

I yield to the chairman now and I will come back again.

Mr. BROWN. Thank you, Mr. Schaefer.

Mr. FISHER. I would just like to, Mr. Schaefer, say and emphasize that these falsified data did not alter the data, and I would emphasize what I said in my preliminary remarks that women in this country do not need to be worried about having a lumpectomy, because not only have we, as I said, our data, but those from around the world and by other people, also indicate that lumpectomy is an appropriate therapy for breast cancer.

Mr. BROWN. Mr. Schaefer?

Mr. SCHAEFER. I am sorry, Mr. Chairman, I have to come back on this one. Well, for you and I, we will never have to worry about whether we decide to have a mastectomy or a lumpectomy, but——

Mr. FISHER. Well, sir, I have two daughters and I have a wife and I have females around me, and I think all of us have to worry, male or female.

Mr. BROWN. Continue.

Mr. SCHAEFER. Yes. We all have a right to know.

Mr. Fisher, you said if your reanalysis had produced evidence that the conclusions of the study were affected by the data alterations, you would have reported those findings immediately. This seems to indicate that it is acceptable to not report findings of fraud unless the fraud is determined to change the findings of the study. Do you believe that?

Mr. FISHER. No, I don't believe that necessarily.

Mr. SCHAEFER. Is it yes or no?

Mr. FISHER. During the—when the material was—we were really under an embargo until the ORI report——

Mr. SCHAEFER. I understand. I am asking you personally.

Mr. FISHER. Yes.

Mr. SCHAEFER. Is it acceptable to not report the findings, yes or no?

Mr. FISHER. No, it is not acceptable to not report the findings.

Mr. SCHAEFER. OK. Well then, the actions of somebody are certainly inexcusable in this situation.

Mr. BROWN. Dr. Fisher, I am still unclear. My understanding is you—you said you removed the bad data, but my understanding is you published papers after that, you submitted papers after that with the bad data in them. Is that not correct?

Mr. FISHER. Those data were included when the biostatistical group and so on decided that there was a need to invoke the intent-to-treat principle which meant leaving in all information.

Now, there is another reason, too, for leaving in all of the St. Luc patients, which I failed to mention, and that is particularly would it—by taking out all of that data, let me repeat that, of the—there were 99 out of 1,500 patients in the St. Luc database which had falsified data. All of these other women were all of the women, and these falsified data related to patient entry information.

But all the women were real patients, real women who all had breast cancer. They were all randomized. They were all followed

up. There was no alteration in the treatment that was given, and one of the things that by taking out all patients prevents you from doing is to determine the toxicities and so on of continued follow up. And that is one of the reasons that the biostatistical community feels very strongly about for leaving patients in.

Mr. BROWN. Didn't you just tell Mr. Schaefer that the bad data was taken out?

Mr. FISHER. It was. In all of the——

Mr. BROWN. Now you are saying some of it was included, you said in response to my question.

Mr. FISHER. In January of 1993, we received a letter from the NCI stating that all of the data should be removed from what we interpreted to be any papers publishing new data, data that had never been published before. Up until that time, we had no guidelines as to not to doing otherwise.

Mr. BROWN. But you had no guidelines not to do otherwise. But don't you know that if you are including this bad data that you at least have some disclosure of it without——

Mr. FISHER. I wish I had the biostatisticians here to address this because it really is an issue which is very strong in the statistical community which indicates strongly that there are ethical considerations and statistical considerations for leaving the data in.

Mr. BROWN. Well, maybe that is some theory that statisticians understand, but don't you disclose that information to the public when, statistics aside, if it is included, don't you disclose it and tell people so that the physicians know?

Mr. FISHER. We couldn't do it with the embargo because it was not permitted to do that because we would have to admit where the data came from. By that time—that was the reason.

Mr. BROWN. You state in your testimony that you complied with NCI's request in January, that no data from St. Luc would be included in publications containing that new data. The subcommittee had a number of manuscripts submitted after that date where St. Luc data was included. Can you explain that discrepancy?

Mr. FISHER. I will have to review that, because I don't know for sure which one.

Mr. BROWN. You were—my understanding is you were the author of this, and you cannot explain it, sir?

Mr. FISHER. Which manuscript are you referring to?

Mr. BROWN. Well, the NCI request in January 1993, JNCI regarding the St. Luc data. You are not aware of that?

Mr. FISHER. January——

Mr. BROWN. It was NCI's request in January of 1993——

Mr. FISHER. That was the letter that came to us, correct, telling us in subsequent publications.

Mr. BROWN. And then the paper was submitted a year later with the bad data.

Mr. FISHER. Which paper?

Mr. BROWN. JNCI.

Mr. FISHER. JNCI. Oh. Are you referring to the paper with endometrial cancer?

Mr. BROWN. Yes.

Mr. FISHER. That paper. Well, that was a paper which was a more recent paper submitted to the JNCI which was the paper in-

dicating the information about endometrial cancer. And that information, in order to—that was providing information relative to the incidence of endometrial cancer and the deaths from endometrial cancer, and that was one of the most important papers I think we have ever done in that it was able, for the first time, to provide some quantification of the risks of getting endometrial cancer in breast cancer patients who received Tamoxifen, and it would, in order to be absolutely certain that we weren't underreporting deaths from endometrial cancer, we included the data from St. Luc Hospital because to have removed the data from St. Luc Hospital would have underestimated the number, could have underestimated the number of deaths from endometrial cancer, and that was what I was referring to previously about when you leave all patients out, you cannot get toxicity or second cancers or this kind of thing. And that was why that was left and that was a very considered decision. It was a decision that was considered—when I say "considered", I mean that it was given a lot of thought and the biostatisticians decided that was the appropriate course of action to take.

Mr. BROWN. So you have ably explained why you left the bad data in there. You have had five statisticians and X number of doctors that knew about this. Why didn't any of you notify the public? Why wasn't there any public disclosure other than these five statisticians and these doctors that knew about it? Why was there not any kind of disclosure?

Mr. FISHER. There is in the paper.

Mr. BROWN. Not offered by you, but ordered by NCI, correct? Is it true, Dr. Fisher, that the paper was submitted without your disclosing that information from St. Luc?

Mr. FISHER. It was true what you say, but the final paper does have it.

Mr. BROWN. In late 1992, the informed consent form for prevention trial participates was amended to state affirmatively that no endometrial cancer deaths had been reported; is that correct?

Mr. FISHER. In late——

Mr. BROWN. In late 1992, that none had been reported due to Tamoxifen?

Mr. FISHER. Yes. To consent form.

Mr. BROWN. By that time, there had been at least one cancer, uterine cancer death known to NSABP, correct?

Mr. FISHER. No, sir. No, that is not so. At the time—at that time there were no incontrovertible cases of endometrial cancer known.

Mr. BROWN. You knew that there was a possibility of perhaps some link between Tamoxifen and the death, but it was not, your word, incontrovertible. So you maybe saw—did you see any link there at all or you just didn't see any absolute connection?

Mr. FISHER. You are talking about one patient who had, and that I think the same patient was discussed previously by previous discussers, and it was a case of a patient who died, a patient died and the death certificate of that patient was that this patient had sepsis due to—we don't need to get into the medical technicalities, although there was a—that this patient actually died of pulmonary embolus and this patient was coded and entered into the system of our system as having died of pulmonary embolus.

And the information was then obtained that this patient had an endometrial—had had an endometrial cancer, and this patient then had a breast cancer. She had an endometrial cancer, she had diverticulitis, she died of pulmonary embolus, and the question was, did she die from endometrial cancer or did she die with endometrial cancer?

We did notify promptly Zeneca at the time of the regular annual report of second primaries of this endometrial cancer, would have been considered a second primary tumor, and they were informed that this patient had died. We reported that on 1-30-92. And then there was some question about whether the patient—you know, again I emphasize, and it has got to be emphasized and reemphasized, that patients with breast cancer who subsequently get endometrial cancer and they die, do they die from the endometrial cancer, do they die from the breast cancer, or what? And it was not until later that we determined that there was most—the death was most likely due to endometrial cancer, but we were never sure. And even today, sir, we are not sure that this first patient died from endometrial cancer, because a recent review of autopsy slides by pathologists, several pathologists have suggested or raised the issue that this patient died, but she could have very well died from breast cancer period, because in the autopsy review they found cells in the bone marrow which were characteristic of breast cancer cells.

And that—so that—we did call that patient a death from endometrial cancer in the report that you referred to about reporting endometrial cancers, the paper, but that is—and that is what is called an endometrial cancer in that paper. But we did report this to ICI as a death from endometrial cancer to Zeneca on 12-13-93, when we felt that the autopsy report became available which said endometrial cancer, but there is still a question about that and about one other death from endometrial cancer where the same situation prevailed.

It is a very, very difficult problem for the pathologists, for the physician to determine whether you have—here you have a woman with breast cancer, she receives Tamoxifen for her breast cancer, and then subsequently she gets an endometrial cancer and subsequently to that she dies. And to say that she dies specifically from endometrial cancer under those terms is very difficult.

And if one goes back and looks at the literature of patients who have been thought to have died in several papers that have been reported, there is evidence that deaths in those papers reported were also related—were difficult to say were due to endometrial cancer and not the breast cancer. So this is—it is really truly a medical dilemma.

I am not—I reemphasize firmly that this was not withheld in any way to conceal a death from endometrial cancer or two deaths from endometrial cancer; it was purely a judgment related to doctors, pathologists, getting data and so on.

Mr. BROWN. Well, I understand as well as a layperson can the complexities of the medical analyses and the difficulty of determining what she might have died of if she had three or four things, any one of which could have caused her death.

How can you affirmatively say in a consent form that she did not die of endometrial cancer, then? How can you say that?

Mr. FISHER. These—the original consent form had—what you are referring to said there were no deaths from endometrial cancer.

Mr. BROWN. Yes.

Mr. FISHER. And that was a—that is an unfortunate thing that sentence got there. The original draft of that consent form did not have that statement, the earlier draft, and then that was there, and that consent form, that statement of no deaths from endometrial cancer—let me just—may I just—do you mind if I just talk a little bit about this, because this is a very difficult problem relative to the consent forms.

I would only say that we were involved completely in the consent form formulations with the pharmaceutical manufacturers, with the NCI, and the NSABP, and the FPA, and others when these various consent forms were formulated.

And as a matter of fact, the statement of no deaths from endometrial cancer put into that consent form, we believe, and have reason to believe, that statement, sentence was put in by the NCI in their review of the—in their—in the preparation of the consent form.

Mr. BROWN. Had you, Dr. Fisher, at the time of that death, when speaking with NCI in understanding what had been the consent in the consent form——

Mr. FISHER. Excuse me, sir. The fact that it said no death was absolutely right as far as we were concerned in that there were no specific deaths at that point in time which the NSA——

Mr. BROWN. So you really didn't know that. If I could, Dr. Fisher, you really didn't know that was the case, you only knew that she could have died from any one of two or three or four causes; you didn't know—you couldn't say which one for sure, you couldn't say which one not for sure.

Mr. FISHER. That is exactly right, and that is why we reported to the Zeneca on 1-30-92 that there was a patient who died, she died and she had that—so that patient was reported. We didn't put in a cause of death because we weren't sure of what the cause of death was. But she was a patient who had died of—actually, the second sheet, these patients were considered a second primary, people who got an endometrial cancer were second primary cancers and they were looked upon as like somebody who would develop a lung cancer or a colon cancer, and they weren't treated any differently.

Mr. BROWN. How many women might have signed up for that study having—having this statement that no one had died of uterine cancer?

Mr. FISHER. I can't answer that, sir. But let me just——

Mr. BROWN. Can you guess? Is it hundreds? Is it thousands?

Mr. FISHER. I just don't know, because I don't know——

Mr. BROWN. How long did the statement remain in there before it was corrected at the prodding of NCI, is my understanding?

Mr. FISHER. We reported the fact—we reported this in October—end of October, October 31, to our group meeting in Chicago. The reports of that case and two other cases were reported, and that was at that time, incidentally, at that meeting, where it was re-

ported Zeneca personnel and NCI personnel were present, they were present, and this was reported at that time.

But the consent form that was in use, the one you are referring to, I would only like to call your attention to the fact that in that consent form, it was vigorously described that there were all kinds of toxicities resulting from the use of Tamoxifen, and it was pointed out that Tamoxifen, women on Tamoxifen developed endometrial cancer in those three times as great, and we also showed that there were deaths from taking Tamoxifen due to blood clots and thromboembolism and other complications. So women going into this study knew that they were taking a drug that did have serious side effects.

Mr. DINGELL. Doctor, can you tell us how long this statement was in effect, that no one had died of endometrial cancer?

Mr. FISHER. Subsequent to the meeting in Chicago which, as I say, was October 31, as I recall, there was—right after that we did meet with the NCI in November, at which time—November or December, at which time the material, a more updated version was presented to the NCI officials, and a plan, an affirmative plan was immediately started to change the consent form. And this was implemented. And again, when we began to do that, make that change, again I would call your attention to the fact that changing a consent form is not—involves many different agencies. It involved the NCI, it involved the FDA, OPRR, it involved the physicians of the NSABP, and so on. So we had a whole long list of people or agencies who wanted to take part in the designing of the new consent form and they all had their own way—intention of what could be done.

At the same time, Zeneca had called to our attention, as did other people, that there were other complications that needed to be put into that consent form, complications which related—things that had to be said in that consent form about pregnancy, about BES, about alopecia, about second cancers, second intestinal cancers, and there was a continuous interplay between all of the people I mentioned, together with all of the people who were interested in getting these various complications into the consent form. This led to continuous dialogue back and forth from our people in the NSABP with all of the government agencies, and virtual gridlock existed.

Mr. DINGELL. All right. Now, Doctor, the purpose of the informed consent form is to see to it that the person who participates in the test knows all of the risks to him or her that are associated with that participation; isn't that true?

Mr. FISHER. Yes, sir.

Mr. DINGELL. That is the whole reason for it. So here, then, for a period of about a year, actually over a year, this form did not indicate the risk of endometrial cancer from the test; isn't that right? Nor did it indicate, nor did it indicate during that period of time that patients were at risk of cancer and possible death from the use of Tamoxifen in connection with this test for a period of better than a year; isn't that so?

Mr. FISHER. No, sir. The consent form did indicate that there was a threefold risk of getting endometrial cancer. That was in the consent form.

Mr. DINGELL. So the—it said the risk of cancer, but it did not say the risk of death of cancer.

Mr. FISHER. No, sir.

Mr. DINGELL. And it may be that people still equate cancer with death, but it may be they don't. But if you just say you get cancer from this, it is not quite as true as saying people have died of cancer from this. So for a period of a year, this form was not brought current with the real state of facts, was it?

Mr. FISHER. It was several months I believe, I am not sure; I don't have the——

Mr. DINGELL. All right. Now, can you name any of the agencies that you said had to sign off on this change who would have objected to assuring the fullest possible information to the participants in the test with regard to the real level of risk?

Mr. FISHER. I am sure they would not have.

Mr. DINGELL. So it is not a realistic assumption that they would have resisted a change which would have better informed the people who were participating in the test, is it?

Mr. FISHER. It wasn't a matter I guess of resisting; it was a matter at the time of the back and forth that had to take place to do it.

Mr. DINGELL. Well, was this question ever laid before the agencies that you referred to? In other words, that you had the additional—that you had deaths from endometrial cancer, was it laid before these agencies or was it not?

Mr. FISHER. Well, certainly I think that it was laid before the agencies, yes.

Mr. DINGELL. Was it laid before them in connection with a request to change the form?

Mr. FISHER. Yes, sir.

Mr. DINGELL. Well, so we have come to the conclusion that for a little over a year that there was no public statement with regard to the risk of death of cancer which came out, nor was there a change in the form during that period. This is from the period late 1992 to early 1994.

How many women signed up for participating in this program during that period of time?

Mr. FISHER. I have lost the thread of the date, sir, I just have lost it.

Mr. DINGELL. A goodly number, a few, none?

Mr. FISHER. A goodly number, I would suspect. I am not sure how many.

Mr. DINGELL. When did you first start signing women up to this particular program?

Mr. FISHER. The program opened on June 1, 1992.

Mr. DINGELL. So that is approximately commensurate with the date that you began to have the information with regard to the risk of death of endometrial cancer?

Mr. FISHER. We had no deaths from endometrial cancer that were confirmed at that time, none.

Mr. DINGELL. How many have signed up now?

Mr. FISHER. As of March, when the study was suspended, there were approximately 11,000.

Mr. DINGELL. How many of them were warned with regard to the possible risk of death from endometrial cancer during this period?

Mr. FISHER. I can't answer that. Their physicians were informed, and it was the job of the physicians to talk to the people about that.

Mr. DINGELL. As a matter of fact, what the people who signed up were told, according to the public pronouncements, was—and the form—that was no one had died of endometrial cancer as a result of this test; is that right?

Mr. FISHER. The consent form said no deaths, but the other thing that consent form—they knew when they were signing that consent form that there were a host of other complications, including endometrial cancer, and there were two deaths that had occurred from thromboembolism, so it wasn't——

Mr. DINGELL. How many of these 11,000 women who signed up for this program were made aware of the two deaths?

Mr. FISHER. These two deaths from thromboembolism? All of them; that was in the consent form.

Mr. DINGELL. All of them were made aware of the fact that there were two deaths?

Mr. FISHER. Yes, sir.

Mr. DINGELL. That is somewhat at variance with your earlier testimony.

Mr. FISHER. Not deaths with endometrial cancer, but deaths of pulmonary embolism or that sort of thing, the point being that all the women who signed up knew that tamoxifen was not a drug which had no side effects whatsoever.

Mr. DINGELL. But we do not quarrel about the fact that they were not told that there were no side effects to its use. We are discussing very specifically the deaths which occurred here. How many were warned of those?

Mr. FISHER. Well, at that time, when the prevention trials started, we had no evidence as far as we can determine that there was specific—that there were patients who died specifically because of endometrial cancer.

Mr. DINGELL. Now, Doctor, the NSABP has provided the subcommittee with a number of documents in the last couple of months. One of these documents is a group of slides dated August 1993. In these slides, there are at least two patients known to NSABP by August 1993 to have died from endometrial cancer, yet information on endometrial cancer deaths was not reported by you to NSABP meetings until late October of 1993, and was not reported to the drug manufacturer until December.

Now, given the fact that the prevention trial was actively recruiting at this time, why was this information not immediately conveyed in August, or earlier, so that the informed consent form could be changed?

Mr. FISHER. Sir, to the best of my ability, I will try to explain that.

The date on the slide was the date at which the Biostatistical Center closes the summary file. Now, what the summary file is, is that is the cutoff point that they use for preparing their information. I myself did not—when the person who made the slide, we put that on, and they usually do because that is the date that is set,

but I myself didn't get that information until the slide was being prepared for the meeting in October, so that is a discrepancy.

It wasn't that I made that slide in August. The slide was not made in August; the slide was made in October.

Mr. DINGELL. Are you telling us that the NSABP didn't tell you about these events? Were you aware or not aware?

Mr. FISHER. To the best of my knowledge, I was not aware of them.

Mr. DINGELL. OK, you were not aware. So then NSABP didn't tell you about these two deaths from endometrial cancer; shouldn't they have told you?

Mr. FISHER. Well, again, the question about the two deaths from endometrial cancer, they should have told me, but there was still some question about whether these were deaths from or with endometrial cancer.

Mr. DINGELL. Well, you didn't know about it, so you didn't say, OK, we ought to look into this and find out. If these things had been brought to your attention, you would have said, we had better look into these things and find out whether these deaths are caused by endometrial cancer or something else; isn't that right? You certainly would have done that if that had been made available to you.

Mr. FISHER. I would have hoped we would have known sooner if there were deaths.

Mr. DINGELL. But they didn't tell you, and they didn't tell the manufacturer.

Now, the manufacturer has got the possibility of lawsuits against him because of the fact that the people have died of cancer from taking this particular substance as part of a test. As a matter of fact, NSABP had the possibility of lawsuits against them, University of Pittsburgh had the possibility of lawsuits against them.

Nobody is notified about the fact that we have these cancer deaths flowing possibly—and I think we might even say "probably"—from the use of tamoxifen. You were not made aware, University of Pittsburgh was not made aware, others in NSABP were not made aware, the manufacturer is not made aware. Is this good administration?

Mr. FISHER. We reported this to the group on October 31st to the——

Mr. DINGELL. And the slide was made in August?

Mr. FISHER. No, the slide wasn't made in August; the slide was made in October. The slide was made in October.

Mr. DINGELL. All right, the data was available in August. When was the slide made?

Mr. FISHER. The slide was made for the meeting in October.

Mr. DINGELL. But the data was available in August then?

Mr. FISHER. The data was—I don't know, I can't answer that.

Mr. DINGELL. It was significantly before the slide was prepared, because the preparation there——

Mr. FISHER. In preparing for the slide——

Mr. DINGELL. Because the data had been around for a while.

Mr. FISHER. In preparing for this meeting, the August 30th data set, that was the cutoff that they used. Now, whether that was known or not known, I don't know.

Mr. DINGELL. Well, here is what the slide sheet on the slide says, it says endometrial cancer, parenthesis, EC, in B-14, as of August 31, 1993. This means that prior to August 31 there was awareness in the test program that this was a problem.

Mr. FISHER. I can't be sure. All I can say is that was when the summary file was closed in the data center—and I apologize for this, and I wish the biostatisticians who were responsible for this kind of thing were here; but they are not here, and I cannot answer the questions.

Mr. DINGELL. Let's go to the next question here.

One argument that has been raised about audits, time limits and the flow of information, is that there is a lack of resources for that function. Is that a problem?

Mr. FISHER. I am sorry?

Mr. DINGELL. Is there a lack of resources for dealing with questions of audits, time limits, and information flow? In other words, do we not have the resources that is needed for that kind of thing?

Mr. FISHER. There was a problem that existed. We—the perennial problem about funding in 1991, when our renewal grant application was submitted, we had asked for $180,000, which then we didn't get; we got $80,000.

Mr. DINGELL. The Chair is going to recognize the gentleman from Colorado, the gentleman from Colorado.

Mr. SCHAEFER. Thank you, Mr. Chairman.

I want to follow up on what the chairman just touched on. This member believes you are a very brilliant doctor, but I am concerned that there was a problem of underadministration. A lot of the information that was flowing out there through audits, et cetera, never seemed to get to you. So, therefore, it seems to me that we needed to add more administration.

Now, did you ever ask NCI for additional funds for administration?

Mr. FISHER. Yes, we did, in the years 1989, 1990, 1991 and so on. We have in our records letters were sent because at that time our program was growing as it continued to grow, and there was either level or reduced funding at each year, and we actually had deficits in our budget, we requested support, and that sort of thing.

Relative to personnel, the addition of personnel, we realized the need to do that. We actually recruited for quality assurance people, people to come in that had the kind of knowledge that could help us. We interviewed four people in the course of a short space of time, or over a period of time, and none of these people seemed to be the kind of people that we would want to have. It is very difficult to get somebody in without any prior experience.

There were other—there—so that those situations did exist.

And let me also add one thing, and that is that Margie McLaughlin, who was the key auditor in the program for 20 years, resigned, retired, and that left the Biostatistical Center with a hole to replace. They had started replacing—training people and so on.

Mr. SCHAEFER. All right. But did you specifically ask NCI for administration funds—not funds for the whole program, administration funds?

Mr. FISHER. I believe so.

Mr. SCHAEFER. You did ask Zeneca for funding. Did you ever approach them on administration-only funding?

Mr. FISHER. No, sir, never did. I would have thought that would have been an improper thing to do.

Mr. SCHAEFER. Well, now I want to get into this reception thing for just a minute. So it is proper for them to pay for receptions, but not for administration funding. They indicated to us that they provided the funds for the receptions. Now, who paid for the travel and lodging?

Mr. FISHER. Travel to group meetings is included in the budget, travel for investigators to go to the group meetings. And I would emphasize that the Zeneca people did—that this is an entirely scientific meeting, the business of the group has no other function, and that meeting is totally for that. And as was explained, there was a reception at each of these meetings.

Zeneca, at the beginning of this thing, sort of, you know, they more or less volunteered to do that years ago. Other pharmaceutical companies made some contributions, and I personally never would go to Zeneca and ask them, will you give us money. We have people that work in my organization who have talked to them and so on.

Mr. SCHAEFER. OK, getting back to the question. I want to understand correctly. Zeneca and others provided funds for the receptions, but the travel to and from wherever it was, the lodging was built into your budget?

Mr. FISHER. Most of the people who came to the meetings paid their own funds for travel, and that came—it could have or it could not have come from what they had been reimbursed for the patient payments, if they had some money left over, which I don't think they did; but that was the——

Mr. SCHAEFER. So it is fair to say, though, that in many instances it was taxpayers' funds that provided this?

Mr. FISHER. Provided investigators to go to the meetings?

Mr. SCHAEFER. Right, lodging and transportation.

Mr. FISHER. Yes, sir.

Mr. SCHAEFER. OK. The fraud on the data was discovered in 1991; am I correct?

Mr. FISHER. Yes, sir.

Mr. SCHAEFER. The embargo was lifted when?

Mr. FISHER. In April of 1993.

Mr. SCHAEFER. OK. When you had these semiannual meetings, after April of 1993, were the people who came to these meetings made aware?

Mr. FISHER. The plan was to present this, as we have said, in a final report; and actually that final report coincided with this current NSABP meeting. That was when it was planned to be done. At that time, the biostatisticians were to have a complete technical report which is in the progress report of this meeting, and that was when the whole thing was to be presented.

Mr. SCHAEFER. OK. When was it presented? Ever?

Mr. FISHER. At this meeting, right now.

Mr. SCHAEFER. So it was actually done?

Mr. FISHER. I presented some of this on Monday, Dr. Redmond and myself.

Mr. SCHAEFER. What Monday? When? What Monday? Just recently Monday?

Mr. FISHER. Day before yesterday.

Mr. SCHAEFER. So after the embargo was lifted in April of 1993, you finally now presented the information that you had fraudulent data?

Mr. FISHER. Yes, sir.

Mr. SCHAEFER. Why this long?

Mr. FISHER. I guess it gets back to what was talked about before, and that has to do with when the issue of the plan was put in and also the other things that—where the results didn't make any difference, and then along came a lot of other things which interfered with going ahead with this paper—at that particular time you were talking about, some of the consent form changes, we mentioned that; the problems with the prevention trial, there were people who were concerned about the prevention trial; the recruitment problems; and there was always something that was coming in which interfered, which seemed to take precedence over presenting this.

Mr. SCHAEFER. Well, maybe a lot of things in your mind did take precedence, but it would seem to me that this information probably should have been at the top of everybody's list, particularly once you tell me that the embargo has been lifted. When it was lifted, I don't see why you immediately could not have notified The New England Journal of Medicine or other comparable publications and gotten this word out as fast as possible.

I might make one final comment here. I don't know what was spent, in taxpayers' dollars, in going to these semiannual meetings and I am sure such meetings are valuable and all that, but maybe some of those dollars could have been better used for administration costs.

Mr. FISHER. Well, sir, let me, if I could, just for a moment, because I think this is terribly important for—at least from my perspective.

When the NSABP started in 1970, when we began—1971 in Pittsburgh—there were 24 members; and today, as you heard, there were over 500 members, and many thousands of physicians, over those years, which have participated. And one of the major goals that I had was to make this a community-based program, not limiting it to physicians.

In the 1970's, there were precious few physicians at cancer centers or major centers who participated in clinical trials, so I spent the next 10 years of my life, or more, trying to convince physicians in the community to participate in the clinical trial program; and I think that worked, and it did work, and community physicians—the quality of medicine through that mechanism has been upgraded. And so the scientific approach to practice of medicine has been improved.

Now, those physicians came to these meetings. They didn't get—and as was made here, comments were made, whatever payments that were given to physicians for—not to physicians, but for the costs of putting patients into clinical trials did not meet the costs that were needed; and I think everybody involved would agree to that, that the cost for a patient in a clinical trial was $800 to $1,000, that sort of range. That money was to be used for a lifetime

of follow-up on those patients. It was a one-time payment, and therefore it took care of the costs of the administrative activity at each one of these community centers where they had to have a nurse, they had to have a data person, and it also paid for following up patients.

This meant that private institutions all over this country and otherwise, other circumstances, were paying for these people, for these patients getting into the clinical trial.

Now, we did have these meetings which, as I say, we had—first of all, the NCI used to—they wanted a meeting twice a year, and we complied for a long time, then it was reduced to once a year.

As this grew and it became a 1,000 to 1,200 or 1,300 people would come to these meetings, we couldn't find places large enough to accommodate 1,200 or 1,300 people, and to keep places where the rates were low enough to be able to afford for all of these people to come; and we are talking about the lowest possible room rates and the lowest possible travel rates, et cetera. And the reason for going around to different places in this country was based on geography—and you talked about Banff in Canada; yes, Canada has been a major contributor to the NSABP. At one time 40 percent of the patients in the NSABP came from Canada, from Vancouver to Montreal. Therefore we needed to have a place to accommodate a thousand or so people, and it had to be in Canada; and we looked for those places and we found that at this particular place we could get a rate which was cheaper than in most other hotels.

Mr. SCHAEFER. OK, but you made the decision then yourself on where to go—Hilton Head, S.C., or to San Francisco?

Mr. FISHER. I think that was done, we had a meeting, our own group had a person who would, you know, find out where the places are, the rates they could get, all of this kind of thing, and that was how it was made.

Mr. SCHAEFER. I would just suggest to the gentleman—I don't know, maybe I am really off base, but Hilton Head, S.C., I don't know if that is the cheapest place to go around or DisneyWorld or the Fairmont Hotel in San Francisco, unless you really pulled some strings.

Mr. FISHER. Well, I would have to—I understand, but I would think that if I could—and maybe I could find out what the rate was that was paid. I have no idea.

Mr. SCHAEFER. OK.

Mr. Chairman, I think I am finished.

Mr. DINGELL. The Chair thanks the gentleman.

Doctor, I have been looking at budget requests here. The total amount of your grant is about $7 million for the assortment of grants that you received; is that correct?

Mr. FISHER. I believe so. Maybe—no, wait, I think that that is for the treatment trial.

Mr. DINGELL. Is that about right?

Mr. FISHER. Treatment, yes.

Mr. DINGELL. Now, in your requests for audit, which is direct cost support for audit function of NSABP, and on 12-1-92 to 1-31-93, the original request was for $181,923, the review committee recommended $115,280; then the final NSABP request budget was

$84,295, so it was cut about 50 percent or thereabouts, down to $84,000.

Now, I note that constitutes about 1 percent of the total amount of the expenditures; is that right?

Mr. FISHER. I don't know.

Mr. DINGELL. If I understand correctly, that would be one auditor and a level of support which might include a modest but not excessive amount of travel or telephones or other support, and probably no clerical assistance or support.

Do you regard that as being an adequate level of audit for a program of this magnitude?

Mr. FISHER. No, sir.

Mr. DINGELL. Now, your final number, then, was $84,295. Now—so that was the final request that was made; that was not just—that was not what the government gave you, that was the final request for budget support.

Now, who was it that made that request? Was that you or was that somebody else?

Mr. FISHER. Well, the $84,000 was not the final request, sir.

Mr. DINGELL. It says here on the paper that I am looking at that the original request, it says original NSABP requested direct cost, then review recommendation level, and then the next column says final NSABP request budget. So that is the request that was submitted, $84,295; and of course you were given that, so you cut it that much before you ever submitted the request.

Who was it that cut those moneys? Was it you or was it somebody else? Did you request it? Who requested it?

Mr. FISHER. Any final fiscal sign-offs were done by me, and I am just not clear on this.

Mr. DINGELL. I am not criticizing the fact that you had a party at the affair that year that amounted to $84,000, but—well, actually $80,000, but it does seem to me that you are more expansive with your expenditure for parties than you are with your auditing.

Mr. FISHER. I don't believe it to be so, sir. I would hate to think that I would be so, after a lifetime of dedication to science, to have thought that I just find absolutely devastating, I really do. I don't think that I——

Mr. DINGELL. Well, all I can say here, Doctor, is this, that according to the sheet which we have, which is a statement here that was submitted to the committee, it says the final NSABP request budget was $84,295, which happens to be exactly the amount you got, so that was the amount you requested. That is for an entire year of auditing, that is for dealing with things like compliance, expenditures of money, seeing to it whether appropriate notice is sent out with regard to changes in risk and things of that kind.

Mr. FISHER. The peer review committee was the one that cut us down, the review recommended level.

Mr. DINGELL. That is interesting because the review committee recommended $115,280, but the final request was $84,000.

Now, who cut it from $115,000 to $84,000? That is a cut of $30,000; that is a cut of about 25 percent. Now, who was it that cut the peer review committee's recommendation? Did you do it? Did somebody else do it?

Mr. FISHER. I will have to let you know, sir. I can't give you——

Mr. DINGELL. Does this appear to have been a wise cut?

Mr. FISHER. No.

Mr. DINGELL. Well, Dr. Fisher, the committee thanks you for your assistance to us.

The Chair notes there is a vote on the Floor. I am going to run over and vote. I will be back in about 15 minutes, and the committee will reconvene then in 15 minutes.

[Brief recess.]

Mr. DINGELL. The subcommittee will come to order. The Chair notes that our next witness is Samuel Broder M.D., Director, National Cancer Institute, National Institutes of Health.

Dr. Broder, welcome to you. Doctor, you are aware of the fact that all testimony taken before this committee is taken under oath. Do you have any objection to testifying under oath?

Mr. BRODER. I understand.

Mr. DINGELL. Given that you are entitled to be advised by counsel during your appearance, do you desire to be advised by counsel?

Mr. BRODER. Certainly not.

Mr. DINGELL. You will note that copies of the rules of the committee, the subcommittee, and the House are there to inform you of the limitations on the powers of the subcommittee as well as your rights as you appear here before the committee.

If you have no objections, then, to testifying under oath, if you will please raise your right hand.

[Witness sworn.]

Mr. DINGELL. Doctor, you may consider yourself under oath. Welcome to the committee.

TESTIMONY OF SAMUEL BRODER, DIRECTOR, NATIONAL CANCER INSTITUTE

Mr. BRODER. Good afternoon, Chairman Dingell and members of the subcommittee. I am Dr. Samuel Broder, Director of the National Cancer Institute. With the Chair's permission, I would like to submit my full written remarks for the record and briefly give an opening statement.

Mr. DINGELL. Without objection, the entirety of your statement will appear in the record. You are now recognized for such additional comments or other comments as you choose.

Mr. BRODER. I will try to be brief.

I am pleased to have this opportunity to bring you up to date on issues discussed at the April 13th hearing regarding the oversight and management of clinical research conducted by the National Surgical Adjuvant Breast and Bowel Project, referred to as NSABP, whose headquarters, as you know, is at the University of Pittsburgh and also to bring you up to date on some of the corrective actions that are being taken to address the problems that this committee has identified and that we ourselves have identified.

Please allow me to state at the outset that progress has been made over the past few weeks in coming to an understanding with officials at the University of Pittsburgh regarding these very serious issues. This is reassuring to us at the National Cancer Institute, as it demonstrates the commitment of the University of Pittsburgh to adhere to the highest ethical, moral and scientific stand-

ards. We particularly acknowledge Chancellor O'Connor and Senior Vice Chancellor Detre, as well as Dr. Ron Herberman.

This commitment has led to certain areas of agreement that we believe will begin to reestablish the public trust in clinical trials in general and in the NSABP in particular.

Specifically, I am very pleased to note the following:

Accrual, or the necessary preludes to accrual for certain key clinical trials has resumed;

New procedures are in place at NCI to deal with scientific fraud or misconduct, especially including more efficient notification to the public;

The NSABP, as a cooperative group, will be recompeted through the usual peer review process;

NSABP is in the process of selecting new scientific leadership and has developed a corrective action plan to address certain problems in management and oversight.

I will briefly address each of these points.

Clinical trials serve as one of the foundation stones of the National Cancer Program. They are the real world test of which new therapies or preventive measures will show benefit for specific patients. The components of all clinical trials include careful and scientifically appropriate protocol design, informed consent, data management control, and publication of trial results. We must have all of these functioning together.

The disclosures of data irregularities in NSABP trials and the lapses of oversight at NSABP headquarters in auditing and reporting trials, including NCI's participation in these matters and in publishing reanalyses of the affected studies with clear disclosure to the reader, raise serious questions regarding the ability of NSABP to perform clinical research. In our system of cancer research, the primary responsibility for the conduct of clinical trials must rest with the grantee, but the National Cancer Institute has responsibilities as well.

To do its job more effectively, NCI has established a new branch to oversee the quality assurance aspects of its clinical trials, and I can provide more details. We have provided more explicit guidelines for auditing and for dealing with irregularities in clinical trials and NCI has undertaken a reevaluation of its quality assurance program and is moving to strengthen key components.

As for NSABP and its leadership, the group has submitted a corrective plan, including provisions for on-site oversight by NCI staff. We have found this plan for resuming certain clinical trials to be generally acceptable, subject to some clarification or modification and certainly subject to continuing oversight. Moreover, all parties, including the University of Pittsburgh, are committed to allowing the peer review process to determine the future location and scientific direction of its clinical trials administration.

Two of our advisory boards, the Division of Cancer Prevention and Control Board of Scientific Counselors and the National Cancer Advisory Board, both recommended in formal votes that accrual for new patients for the Breast Cancer Prevention Trial with tamoxifen be resumed as soon as possible. In addition, on June 7, 1994, the Oncologic Drugs Advisory Committee of the Food and Drug Administration reviewed the recent information regarding

endometrial cancer deaths and other information and concluded the tamoxifen Breast Cancer Prevention Trial should continue, and also recommended that accrual be resumed.

Unlike most treatment trials, the prevention trial requires risk assessment as the first step, but risk assessment does not mean an immediate assignment to either placebo or tamoxifen, as the process requires roughly one month's lead time. In general, resumption of accrual and risk assessments will be allowed at NCI-designated cancer centers, formal members of our Community Clinical Oncology Program—the so-called CCOP's, which are different from NSABP—and in the case of NSABP members, certain institutions with an acceptable audit record in the past 3 years.

I will not review the entire history of the events that have led us to this point, as many issues have been addressed in previous testimony. I would like to bring to your attention several additional irregularities that have been identified at a few participating NSABP institutions. The problems range from incomplete record-keeping to deficient informed consent procedures. Following that, I would be grateful for permission to highlight a few of the main facts and steps that we have taken to strengthen some of our procedures.

At the last hearing, we informed you about the issue of serious data irregularities at St. Mary's Hospital in Montreal. The problem had been noted by NSABP in September of 1993, but was not brought to NCI's attention. In fact, NCI staff independently discovered the documentation regarding this problem in March of 1994 during our site visit to NSABP headquarters. Currently, the Office of Research Integrity is still investigating this institution, but I believe that there are data falsifications involved.

Another of the institutions is the Memorial Cancer Research Foundation in Los Angeles, where NCI conducted an audit on April 29th and 30th at the request of the local principal investigator, following contact by a news reporter. Files for NSABP patients enrolled on the B-06 study of breast-sparing surgery and those of other patients were reviewed by the NCI auditors. The major areas of concern noted by the NCI auditors included patient eligibility, the randomization process and the obtaining of informed consent.

These findings confirmed the findings of the NSABP's own audit report of 1990 that a serious problem had been identified regarding the accuracy of the data reported at randomization.

It is of note that neither the investigator in Los Angeles nor the National Cancer Institute had been notified of the concerns identified in the 1990 NSABP audit report, nor had there been any follow-up action by NSABP to correct these problems. We have been informed that the NSABP report, in fact, languished in obscurity in an unmailed envelope in the NSABP files. Correspondence from NSABP provided to the auditors appeared to or actually did congratulate the principal investigator in Los Angeles on the status of follow-up cases. This is incomprehensible to us.

This matter has been referred to the Office for Protection from Research Risks, OPRR, and the local Institutional Review Board, which we abbreviate as IRB, because of concerns about possible breaches of patient confidentiality and patients not having been provided, or not having been given an opportunity to provide a

truly informed consent; and to ORI, for issues related to the scientific conduct of the trial.

Other problems include South Nassau Hospital on Long Island, where patients were enrolled despite questionable eligibility. NCI had been given verbal notification that the NSABP had suspended the institution in follow-up to the audit report. However, from what we can tell, this was never done and none of the additional follow-up reports were provided to us.

I want to echo Chancellor O'Connor's comments that you heard earlier regarding the important contributions of this committee's staff in helping us identify and sort through these very complex issues.

Other NSABP audit sites such as Tulane and Louisiana State University demonstrated certain data management deficiencies. NCI has conducted two audits at each of these sites. At the initial audits, which were arranged with essentially no advance notice, there were substantial portions of missing data on eligibility and other matters, perhaps due in part to the shortness of the notice; but in all measures, this was an unacceptable site visit situation.

Both institutions have developed new data management plans and have taken corrective actions to ensure that these kinds of problems are minimized or don't occur in the future. In the case of Tulane, we have tentatively agreed on a conditional resumption of accrual based on their recruitment of a new leader for clinical trials, the development of a comprehensive data management system, and also provided that they expeditiously clear up outstanding delinquent data and residual issues from the May 1994 audit. They must also make adequate provisions to ensure the performance of their affiliates, and they must agree and have agreed to a reaudit in roughly 6 months.

We hope that a similar plan can be worked out for Louisiana State University.

The NSABP uses as its testing ground real surgeons, the kind of individual seen by the average American when they seek treatment for cancer. However, this characteristic, which is a virtue in many ways, can also pose special challenges for adhering to data management and reporting requirements.

For our part, NCI requested changes in NSABP audit procedures, including on-site auditing, auditing more patient charts and providing to NCI fixed annual audit schedules long before these issues had become front page news. Unfortunately, NSABP did not comply, and NCI staff did not take action to compel compliance.

Regrettably, our staff routinely accepted late reports from NSABP with their promissory notes to do better in the future, or with their explanation that the responsibility for conducting high-priority studies had strained their ability to issue timely reports, or sometimes with no explanation. This will not happen again.

The NSABP probation period requires submission of an audit schedule for the coming month, the performance of on-site audits and the auditing of 10 percent of all charts. Timely reporting is required; I believe we have their attention. An electronic system for alerting NCI staff to expect and to review site visit reports for all cooperative groups is being established.

I would like to very briefly turn to one other area. As of June 10, 1994, 287 of 293 Institutional Review Boards have reviewed and approved the revised protocol and consent form, and approximately 3,000 patients have signed the revised consent in connection with the tamoxifen studies that we have discussed earlier. There is a "Dear Participant" letter that was targeted to all women and was required as of April of 1994; and we will explore other ways of communicating directly with the women in our studies.

Finally, we have initiated recovery of funds in instances where scientific fraud or misconduct was identified. Recovery of funds in cases of a finding of scientific fraud or misconduct is now standard operating procedure at the National Cancer Institute and is one of the action items in our manual issuance on this topic.

Also, the University of Pittsburgh has been instructed to provide criteria for ineligible or inevaluable patient accrual that would be subject to reimbursement under a condition of the grant that has been in place since April of 1993—again, before these issues became newspaper items.

Mr. Chairman, this has been a very difficult time for everyone involved in the events that have occurred over the past few months. There has been much criticism of all parties involved and much concern about the future. We have listened carefully to these comments and will do our best to address them. All of us, especially those in the scientific community, must keep in mind that the uncertainties and challenges we face in these matters amount to nothing compared to what the average cancer patient must face.

Cancer patients and their loved ones are our constituency.

Thank you for the opportunity to appear before you today.

[The prepared statement of Dr. Broder follows:]

Statement of Samuel Broder, M.D.

Good morning, Chairman Dingell and members of the Subcommittee. I am Dr. Samuel Broder, Director of the National Cancer Institute. With me today are Dr. Bruce Chabner, Director of the Division of Cancer Treatment, Dr. Michaele Christian, Acting Chief of the Clinical Trials Monitoring Branch, DCT, and Dr. Leslie Ford, Acting Deputy Director of the Division of Cancer Prevention and Control, NCI. I am pleased to have this opportunity to bring you up to date on issues discussed at the April 13 hearing regarding the oversight and management of clinical research conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), whose headquarters is at the University of Pittsburgh, and the corrective actions that are being taken to address these problems.

Please allow me to state at the outset that progress has been made over the past few weeks in coming to an understanding with officials at the University of Pittsburgh regarding these very serious issues. This is most reassuring to us at NCI, as it demonstrates the commitment of the University of Pittsburgh to adhere to the highest ethical, moral, and scientific standards. We particularly acknowledge Chancellor O'Connor and Senior Vice-Chancellor Detre, as well as Dr. Ron Herberman. This commitment has led to certain areas of agreement that we believe will begin to re-establish the public trust in the clinical trials process of the NSABP.

Specifically, I am pleased to note the following:

1. Accrual for certain key clinical trials has resumed;
2. New procedures are in place at NCI to deal with scientific fraud or misconduct;
3. The NSABP, as a cooperative group, will be recompeted through the usual peer review process;
4. NSABP is in the process of selecting new scientific leadership and has developed a corrective action plan to address problems in management and oversight.

I will address each of these points in greater detail.

Clinical trials serve as one of the foundation stones of the National Cancer Program. They are the real-world test of which new therapies (or preventive measures) will show benefit for specific patients. The key components of all clinical trials include careful and scientifically appropriate protocol design, informed consent, data management, quality control, and publication of trial results based on thorough statistical analysis. When all of these components are in place and functioning smoothly, we can have confidence in the results of clinical trials. When one or more of these components breaks down, we must identify the problem as quickly as possible and take action to repair it. The disclosures of data irregularities in NSABP trials and the lapses of oversight at NSABP headquarters in auditing and reporting trials, and in publishing reanalyses of the affected studies with clear disclosure to the reader, raised serious questions regarding the ability of NSABP to produce valid research. The primary responsibility for the conduct of clinical trials must rest with the grantee. But NCI has responsibilities as well.

To do its job more effectively, NCI has established a new Branch to oversee the quality assurance aspects of its large-scale clinical trials. More explicit guidelines for auditing and for dealing with data irregularities in clinical trials have been set in place, and NCI has undertaken a re-evaluation of its quality assurance program and is moving to strengthen key components. As for the NSABP and its leadership, the group has submitted a corrective plan of action, including provisions for on-site oversight by NCI staff. NCI has found this plan for resuming trials to be generally acceptable subject to some clarification or modification and continuing oversight. Moreover, all parties--including the University of Pittsburgh--are committed to allowing the peer review process to determine the future location and scientific direction of its clinical trials administration.

Accrual has been opened at selected sites to certain key clinical trials. For selected treatment trials in breast cancer and rectal cancer, this means patients may be entered into trials immediately. Two of our advisory boards, the Division of Cancer Prevention and Control Board of Scientific Counselors and the National Cancer Advisory Board, both recommended in formal votes that accrual for new patients for the Breast Cancer Prevention Trial with tamoxifen be resumed as soon as possible. In addition, on June 7, 1994, the Oncologic Drugs Advisory Committee of the Food and Drug Administration reviewed the recent information regarding endometrial cancer deaths and other information and concluded that the tamoxifen Breast Cancer Prevention Trial should continue, and recommended that accrual be resumed. Unlike most treatment trials, the BCPT requires risk-assessment as the first step, but risk assessment does not mean an immediate assignment to receive either placebo or tamoxifen, as the process requires at least one month's lead time. In general, resumption of accrual and risk assessments will be allowed at NCI-designated Cancer Centers, formal members of the Community Clinical Oncology Program (CCOPs), and in the case of NSABP members, certain institutions with an acceptable audit record in the past three years.

Currently NSABP is in the process of choosing new scientific leadership and has informed us that they hope to complete that process by September 1, 1994. As you know, Dr. Ron Herberman has been acting as the interim chairman of NSABP. Once the new leadership is in place, we hope to allow roughly one year to permit all potential grantee-competitors to prepare grant applications for components related to statistical support, auditing, etc., and submit them for peer review.

With your permission, I will not review the entire history of the events that have led us to this point as many issues have been addressed in previous testimony; however, I would like to bring to your attention several additional irregularities that have been identified at a few participating NSABP institutions. The problems range from incomplete record-keeping to deficient informed consent procedures. Following that, I would like to highlight a few of the main facts and the steps we have taken to strengthen some of our procedures.

At the last hearing, we informed you about the issue of serious data irregularities at St. Mary's Hospital in Montreal. The problem had been noted by NSABP in September 1993 but was not brought to NCI's attention. In fact, NCI staff independently discovered the

documentation regarding this problem in March 1994 during our site visit to NSABP headquarters. Currently the Office of Research Integrity (ORI) is still investigating this incident.

Another of the institutions is the Memorial Cancer Research Foundation in Los Angeles, California, where NCI conducted an audit on April 29-30, at the request of the local Principal Investigator following contact by a news reporter. An NSABP audit of this institution had been conducted and a report prepared on April 3, 1990; however, apparently neither the Principal Investigator in Los Angeles nor NCI had been provided with a copy of the report, which identified several inconsistencies and incomplete records. Files for NSABP patients enrolled on the B-06 study of breast-sparing surgery, and those of other patients, were reviewed by the NCI auditors. The major areas of concern noted by the NCI auditors included patient eligibility, the randomization process, and the obtaining of informed consent. These findings confirmed the findings of the NSABP's own audit report of 1990 that a serious problem had been identified regarding the accuracy of the data reported at randomization.

Neither the investigator in Los Angeles nor NCI had been notified of the concerns identified in the 1990 NSABP audit report, nor had there been any follow-up action by NSABP to correct these problems. We have been informed that the NSABP report was attached to an unmailed envelope in the NSABP files. In fact, correspondence from NSABP provided to the auditors congratulated the Principal Investigator on the status of follow-up cases. This matter has been referred to the Office for Protection from Research Risks (OPRR) and the local Institutional Review Board (IRB) because of concerns about possible breaches of patient confidentiality and patients not having provided informed consent, and to ORI due to issues related to the scientific conduct of the trial.

Other problems include South Nassau Hospital on Long Island where two patients were enrolled despite questionable eligibility. NCI had been given verbal notification that NSABP had suspended the institution in follow-up to the audit report; however, this was apparently never done and none of the additional follow-up reports were provided to us. [Perhaps I could take this opportunity to acknowledge the diligence and effectiveness of your staff in helping us identify and sort through these issues.]

Other NSABP audit sites such as Tulane and Louisiana State University demonstrated certain data management deficiencies. NCI has conducted two audits at each of these sites. At the initial audits, which were arranged with no advance notice, there were large amounts of missing data on eligibility and other matters due in part to unavailable charts. When we returned in May after more notice, the majority of charts and missing data had been located and were available for review. In addition, both institutions have developed new data management plans and taken corrective actions to ensure that these kinds of problems don't occur in the future. We have tentatively agreed to a conditional resumption of accrual at Tulane, which developed a comprehensive data management system, providing that they: expeditiously clear up outstanding delinquent data and residual issues from the May 1994

audit; make adequate provisions to ensure the performance of their affiliates; and agree to a reaudit in six months. We hope that a similar plan can be worked out for LSU once we have received additional details regarding their corrective plan.

One of the difficulties we faced was that NSABP, one of nine major clinical trials cooperative groups, had a philosophy of using a less stringent auditing system than the other groups. This was due to several factors, including the very large, community-based surgical membership of NSABP, its long history of productivity, its proud reputation, and its insistent adherence to its own traditions for auditing and quality control. The community-based nature of NSABP surgeon participants is one of the group's greatest strengths: Their results reflect the ability of community-based surgeons to apply new treatments and new surgical methods. The NSABP uses as its testing ground the real doctors who the average American will see when seeking treatment. However, this same characteristic also can pose special challenges for adhering to data management and reporting requirements.

For our part, NCI requested changes in NSABP audit procedures including on-site auditing, auditing more patient charts, and providing to NCI an annual audit schedule. Unfortunately, NSABP did not comply and NCI staff did not take action to compel compliance. Regrettably, our staff routinely accepted late reports from NSABP with their explanation that the responsibility for conducting high priority studies had strained their ability to issue timely reports, or sometimes with no explanation. This will no longer happen. The NSABP probation period requires submission of an audit schedule for the coming month, the performance of on-site audits, and the auditing of ten percent of all charts. Timely reporting is required. An electronic system for alerting NCI staff to expect and to review site visit reports for all cooperative groups is being established and will be operational within 90 days. In addition, we have met with the Clinical Cooperative Group chairmen, who have agreed that there should be common standards for all groups in terms of what constitutes an acceptable audit. These criteria are being developed in conjunction with the groups and will be incorporated into the new NCI on-site monitoring guidelines. Adherence to these criteria is included in the terms of award for all cooperative group grantees. I should point out that these will represent minimum criteria, and individual Groups would certainly have the option to impose additional (more stringent) requirements for their member institutions.

There will also be cooperative group-wide standards for auditing, reporting audit results, and dealing with instances of fraud or misconduct, as well as a group-wide requirement for ethics training and for credentialing new investigators.

We have met with officials from the group and from the University of Pittsburgh to discuss how the remaining problems can be addressed. Several specific items have been discussed and agreements reached between NCI and the University of Pittsburgh:

- We are informed that NSABP accepts the idea that its management needs improvement, and the Chancellor of the University of Pittsburgh has issued an apology for that institution's role in these problems;

- The University of Pittsburgh will resolve the inconsistency found as a result of the EMMES reanalysis of the B-06 (breast-sparing surgery) study between data and published journal articles regarding ipsilateral recurrence of breast cancer (i.e. recurrence in the same breast);

- Each week, NCI staff will be on-site at NSABP headquarters in Pittsburgh to enhance cooperation efforts and to provide oversight. Pittsburgh will provide appropriate space;

- NCI has raised concerns regarding remaining problematic issues, including a 1993 memorandum from Dr. Carol Redmond to Dr. Bernard Fisher noting her serious concerns about protocol design and informed consents, and we expect a response from NSABP; and

- The University is proceeding with a broad inquiry into NSABP administrative issues, data irregularities, and human subjects protection in coordination with the Office of Research Integrity and the Office for Protection from Research Risks.

The NCI is committed to working with the University of Pittsburgh and the new leadership of NSABP to ensure that research continues under careful and appropriate scientific and administrative oversight. We believe that the leadership of the NSABP should be given an opportunity to heal any remaining wounds, galvanize the membership, and develop and implement a scientific agenda. It is possible that there would be a physical relocation of the operations and statistical offices to new institutions and new sites. The operations offices of other cooperative groups have relocated in the past, and there are precedents for having the chair and the statistical center located at different sites. If this were to happen, the NCI on-site presence at the University of Pittsburgh would help expedite the process. But, once again, we are committed to allowing the principles of open competition and peer review to resolve these kinds of issues.

We are still in the process of conducting a detailed audit of the B-06 (breast-sparing) study. Institutions that contributed 10 or more patients to the B-06 study, which accounts for approximately 1500 patients, will have been audited most likely by August. An NCI contractor will then conduct an independent statistical reanalysis. We estimate that this re-analysis will be completed by late summer or early fall, but I cannot absolutely promise this as a deadline.

NCI staff are coordinating certain activities with the DHHS Office of the Inspector General. This will likely include reviews that will compare the research records at the NSABP statistical center with the computerized database used to analyze the study to ensure no errors or bias were introduced at the statistical center.

I would like to return briefly to the Breast Cancer Prevention Trial. One of the criticisms of this trial has been the lack of completeness and promptness of the informed consent process.

NCI has an obligation to provide accurate, up-to-date scientific information to patients who participate in our studies. We have taken some steps to quicken the process and we are exploring other new ways of communicating directly with patients to inform them of changes to informed consent. On April 18, as instructed by NCI, NSABP sent a notification to all participating sites that they must convey a "Dear Participant" letter to all BCPT participants by April 22, 1994. This step was intended to ensure that all women participating in the BCPT would have immediate notification regarding the information that had been distributed to the participating centers in January 1994. We felt this was necessary because the usual and customary process being followed, including review and approval by the local IRBs, is a lengthy one and many women had not been contacted directly. The information provided to women in the "Dear Participant" letter was the same as that included in the Zeneca "Dear Doctor" letter dated April 8, 1994. In addition to requiring direct notification to participants, we also are monitoring the reconsenting process very closely. Following instructions issued by the Office from Protection of Research Risks in November 1992, each IRB was provided with the full NSABP protocol and consent form, as well as the local institutions's version of the consent form.

As of June 10, 1994, 287 out of 293 institutional IRBs have reviewed and approved the revised protocol and consent form, and 2,957 patients have signed the revised consent form. As I mentioned a few moments ago, however, all women participating in the trial were targeted to receive notice of the changes as of April 22, 1994.

We will continue to explore novel ways of communicating new information to patients quickly. One approach we are testing involves an electronic bulletin board that may be available in some doctors' offices or participating hospitals where patients could browse through information updates or even electronically indicate their "re-consent" after having read new information and discussed it with appropriate medical staff. We will explore many options to make more information available to patients more rapidly, and no single method is likely to serve all of our needs.

Finally, we have initiated recovery of funds in instances where scientific fraud or misconduct was identified. Recovery of funds in cases of a finding of scientific fraud or misconduct is now standard operating procedure at the National Cancer Institute and is one of the action items in our manual issuance on this topic. Also, the University of Pittsburgh has been instructed to provide criteria for ineligible or inevaluable patient accrual that would be subject to reimbursement under a condition of the grant award that has been in place since April, 1993.

Mr. Chairman, this has been a very difficult time for everyone involved in the events that have occurred over the past few months. There has been much criticism of all parties involved and much concern about the future. We have listened carefully to these comments and will do our best to address them. In this process, our advisory groups have been most helpful. All of us, especially those in the scientific community, must keep in mind that the uncertainties and challenges we face in these matters, amount to nothing compared to what the average cancer patient must face. Cancer patients and their loved ones are our constituency. I believe that the result will be a stronger and more responsive clinical cooperative group program made up of dedicated, caring, principled scientists and physicians. We must expect nothing less.

Thank you for this opportunity to appear before you today.

Mr. DINGELL. Dr. Broder, the committee thanks you for your very helpful testimony.

The Chair recognizes now my good friend from Colorado for such questions as he chooses.

Mr. SCHAEFER. Thank you, Mr. Chairman.

Dr. Broder, the tamoxifen trials have been resumed, as I understand it. Do you believe that NSABP is capable of monitoring these trials at the present time?

Mr. BRODER. Yes, I do. We will have oversight and we will have an individual up there a certain portion of the time, physically on site. They have provided us or have assured us that there will be space, and we believe that they—based on a number of things that they presented to us privately and in some of the testimony that you have heard—have a sincere commitment to this issue, and I believe that they have a can-do spirit and they will comply with us and comply with the needs of the public and with the interests of the Congress.

Mr. SCHAEFER. I am sure that this committee, as well as a lot of the people in this country, agree that they have a new spirit, that we aren't going to get into the same problems all over again. What type of person are you going to have up there? Are you going to have a physician there or a doctor?

Mr. BRODER. We will try to have a professional full-time employee of the National Cancer Institute up there a certain amount of time. I can't tell you the individual will be there 7 days a week, 24 hours a day, but there will be an individual up there, and we will probably have a certain schedule or rotation since we, at the current time, cannot detail a single individual.

We will probably establish a rotation to have an NCI professional on site periodically to oversee and to interact and to make sure that we are in full compliance with all of the issues, and that we are correcting the problems that have been identified.

Mr. SCHAEFER. In your opinion, does NSABP currently have capabilities to conduct their audits and generate audit reports that change that much that they can do that now?

Mr. BRODER. Thank you for the question, Mr. Schaefer.

I want to make a point very briefly that while there are going to be some exceptions to what I am going to say, many of the issues that we have dealt with today were not necessarily the fault of the actual hands-on people doing the audits. Miss McLaughlin, for example, was a career employee doing audits. In my opinion, at least from what I can tell—and I would be prepared to be informed otherwise if I am wrong—basically she told it like it was when she encountered problems; though we certainly should improve the audit process and the scheduling and so on.

But the actual hands-on performance of the audits is not so much of the problem as what was done with the information, once gathered. I believe this is a recurring theme, that perhaps most of the staff that worked with me on this matter would agree, that there is an identification of a problem, it is sitting there, it stays in a file, and there appears to be no action and no apparent explanation for the inaction. So I believe that it is a matter of philosophy as much as it is resources and the commitment. You have to want to act on your information.

Mr. SCHAEFER. Right. I am sure you heard testimony just prior to this as regards these audit reports. Too many times, as I certainly understand it, they didn't reach the point where they should have. So all of this information sitting out there as to all of these various problems that we have, and it never reached the proper people.

Mr. BRODER. Either it didn't reach the proper people or for whatever reason, perhaps well justified or not, appropriate decision-making was not based on the facts as they were available.

Mr. SCHAEFER. Do you believe that they are understaffed as far as the administration level goes?

Mr. BRODER. I do not believe that they are understaffed, and I am not sympathetic, at least excessively sympathetic to the argument that most of the problems that we have heard today are focused on resources.

Yes, if you were at an appropriations hearing, I would certainly give you a very good defense of why we need a budget and why we need certainly the President's budget. But I don't believe that most of these issues that we have encountered today are focused on resources per se, and I actually feel that is taking us a little bit away from the point.

Mr. SCHAEFER. So just with a little bit of streamlining in the present system, it could probably do the job without——

Mr. BRODER. Well, I don't want to say that resources aren't relevant; they are always relevant, as we can certainly discuss, and I will also get into the issue of resource allocation should you wish me to, but I think that it is basically a philosophy, which also has to be a part of the process.

We have to, without fear of favor, as much as human beings can, accept data as they come in. That is what a scientist really must do, and auditing from my point of view is a specialized kind of science. You have to take the facts as they come in, not as you want them. It is very dangerous for a scientist or a doctor to ignore facts, and I think that in this situation, the recognition of the facts as they came in, and an appropriate decision-making process after those facts were known would have gone a long way to obviate many of the problems that we have.

Mr. SCHAEFER. Well, at our April hearing, Dr. Friedman testified that two people had been added, assigned to the monitoring of the reports that came in from the University of Pittsburgh, and he stated he thought this was inadequate. Is that your opinion or can you even make an opinion?

Mr. BRODER. Are you asking whether we at NCI should be allocating more resources?

Mr. SCHAEFER. No. Well, I am just saying, he stated that two people added is inadequate, it is not sufficient.

Mr. BRODER. I agree with that, but in agreeing with that I want to acknowledge that many of the problems which this committee has identified and that we have discussed or that NCI itself have identified are not linked to a resource issue.

Yes, resources are necessary, and I pride myself in being pretty good in making a case for more resources, but I don't believe that is an issue before us today. Many of the issues that were identified earlier had to do with not acting on information as it came in, in-

formation that auditors had picked up, information that was in a file—memos that one investigator at NSABP would write to another investigator without a follow up. I believe that there were a lot of decision-making issues.

We heard earlier today discussions about endometrial cancer deaths. I don't believe resources are the issue that we were talking about.

Mr. SCHAEFER. OK. You also probably heard me—I referred, and the chairman did too, to this embargo thing in a couple of cases which prevented NSABP from announcing the presence of fraud in studies. Do you know under what authority such an embargo can be initiated?

Mr. BRODER. I would answer that in two ways. First, the embargo is a request of a sister agency of the Public Health Service to not interfere with an ongoing investigation, and I understand the responsibilities that ORI has in this matter, but I believe you and others on the committee very carefully pointed out that the embargo ended approximately in April of 1993, and well prior to the ending of the embargo, NCI and ORI staff had communicated to the NSABP that we expected an analysis published that would exclude the Poisson data and provide a notice to the reader.

What we are talking about is an ethics issue, not a statistical issue. It is a notification to the reader; it is a disclosure to the reader that there is a problem.

We had received assurances that the process was working and that a paper was being prepared. It was a surprise to us to learn that in fact, did not occur, and, please, I might want to add one other thing.

There was a publication that came out in June of 1993 which excluded the data from the St. Luc's site. There was a galley proof still available in April of 1993. The individual patients from St. Luc's Hospital appear to have been removed without a disclosure to the reader.

So those are just the facts as I know them, and I have had discussions with the editor of the New England Journal of Medicine on this topic. So it is certainly possible to argue, as you have successfully done, that there were substantial delays here, and we are sorry for them.

Mr. SCHAEFER. It gets back to the people's right to know, as we indicated.

One final question, Mr. Chairman. Was NCI responsible for altering the consent form as Dr. Fisher alleges?

Mr. BRODER. The NCI submitted an informed consent in response to a request by the Food and Drug Administration to specifically address the mortality implications of endometrial cancer, and relied on Dr. Fisher's and others' presentation of information from their database. They were asked were there endometrial cancer deaths and we were told no. We must rely on the grantee in these matters. I believe it was a joint decision.

Mr. SCHAEFER. So was it only because Mr. Fisher had not reported the deaths?

Mr. BRODER. Well, as you heard his testimony today, he agreed with the inclusion of the statement, and from his point of view, it was valid as of the time of the insertion. Had we known then what

we know now, that statement would not be in there, and I submit to you that the grantee has a duty to inform us.

One of the things that I noticed in the testimony up until now is that there was a great deal of discussion about reporting to Zeneca, the pharmaceutical company, and so on and so forth. As they said in Cool Hand Luke: What we have here is a failure to communicate. And basically I think that we should have known that there were deaths. We are the grantor, and if there are difficulties of sorting them out, then we will be happy to participate.

I don't think it is appropriate for us to learn at a scientific meeting as the company has expressed, that there is a new and unreported side effect. That puts us in the status of just another participant in the study, and I reject that concept. We are the grantor.

Mr. SCHAEFER. So you didn't know what Dr. Fisher knew.

Mr. BRODER. We learned at the public presentation, which was at the end of October.

Mr. SCHAEFER. Yes. I couldn't agree with you more on that last one.

Mr. DINGELL. The Chair thanks the gentleman.

Dr. Broder, the Chair would like to thank you for your very helpful testimony to us today. We always are appreciative of your kindness and the very fine job you are doing at NCI.

You appeared before the subcommittee approximately 2 months ago and were aware of the problems in the NSABP trial sites at St. Luc's and were beginning to learn about the problems at St. Mary's. Based on your testimony today, it appears that NCI has learned a lot more about the management and operations at NSABP and its sites since that time.

Can you characterize for the subcommittee what you found regarding the management and operation at NSABP and its sites, please?

Mr. BRODER. I think on balance, we have observed that we must have a more organized and objective set of criteria for who can be a participating member; we must have more effective follow up and communication with the participants; we must have a process in which problems are identified quickly, and basically, if possible, corrected by the grantee, not simply corrected by the NCI coming in on an emergency basis. The final responsibility for these issues must lay with the grantee.

I think that those are the major issues, that basically we must have a more organized and effective method of adhering to protocol eligibility and to following the clinical trials as they are designed. And I think we are working in that direction.

I think Dr. Herberman has expressed an extreme commitment to this point, and I am rather pleased with the direction that he has been able to do an interim principal investigator.

Mr. DINGELL. Now, Doctor, we have heard a number of explanations as to why the problems have occurred. For example, lack of audit resources, and it does appear that there is a deficiency here; lack of an executive director to handle management administration; that the trials grew too quickly. I would like to get your thoughts with regard to the matters before the committee today.

First, with regard to the issue of lack of audit resources, did NCI underfund audit requests made by Pittsburgh?

Mr. BRODER. The short answer is no. I will elaborate if the Chair asks, but the answer is no, and I will provide you with the information either now or for the record.

[The following information was received:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

MEMORANDUM

DATE: June 14, 1994

FROM: Section Chief, GAB, OAM, NCI

SUBJECT: NSABP Audit Support

TO: Chief, GAB, OAM, NCI

The following represents a comparison of the funds requested, recommended and awarded on CA12027-20, 21, 22 and 23 and CA37377-07, 08 and 09 for NSABP staff on-site audits of the NSABP participant institutions. It also includes a comparison of the amounts awarded and expended for CA12027-21, 22 and 23 and CA37377-09 for audit travel. (To date, we have not requested expenditures for years 07 and 08 on CA37377.) I have indicated the FY involved and the budget period.

Attachment 1 compares the direct cost support requested by NSABP for the audit functions to the amount recommended by peer review, the amount subsequently requested by NSABP in response to NCI funding plans or Type 5 committed levels, and the amount awarded by NCI for audit functions for CA12027-20, 21, 22 and 23 and CA37377-07, 08 and 09.

In Attachment 2, I have provided a comparison of the funds awarded for audit travel to the reported NSABP expenditures of travel funds for years 21, 22 and 23 of CA12027 and year 09 of CA37377. This is the information requested of Mr. Crouch in our April 8 and June 2 letters. The reason for reflecting only the travel amounts is that for the 21 and 22 years of CA12027, figures were only provided for the expenditures on travel. However, in the report on the 09 year of CA37377, he indicates budgeted and expended funds for auditors. In our review of the file, we can not find reference to a request for salaries specifically for auditors, so I have removed those amounts from the reported expenditures to allow comparability of cost pools. (The budgets for CA12027 included salaries and other costs and, therefore, those figures are included in Attachment 1.)

I have attached copies of the information that Michael Crouch provided in response to our requests of April 8 and June 2, 1994, in which we asked for a description of the audits which were planned for each year as compared to the audits which were actually performed and the associated cost of each audit.

If additional information is required, please let me know.

ATTACHMENT 1
DIRECT COST SUPPORT FOR AUDIT FUNCTION OF NSABP

PROJECT/YEAR	ORIG. NSABP REQUESTED DIRECT COST	REVIEW RECOMM. LEVEL	FINAL NSABP REQ. BUDGET	NCI AWARDED DIRECT COST
CA12027-20 FY 91 (2/1/91-1/31/92)	$ 52,076	Unavail.	$ 76,413	$ 71,838
CA12027-21 FY92 (2/1/92-1/31/93)	181,923	115,280	84,295	84,295
CA12027-22 FY93 (2/1/93-1/31/94)	192,095	Unspecified	90,100	84,466
CA12027-23 FY94 (2/1/94-1/31/95)	202,851	Unspecified	185,960	174,803
CA37377-07* FY91 (8/1/91-5/31/92 Ten months)	41,459	Unspecified	21,555	21,555
CA37377-08* FY92 (6/1/92-5/31/93)	Unspecified	Unspecified	49,759	45,136
CA37377-09* FY93 (6/1/93-8/31/94)**	Unspecified	Unspecified	92,923	90,750
TOTAL			$601,005	$572,843

* Requested support for travel only.
** 09 year extended at no-cost for 3 months from 5/31/94 to 8/31/94.

Definition of Columns
Column 1 - Original requested levels found in application. If no detail was provided in the competing application for specific amounts requested for audit support in future years, then unspecified is indicated.

Column 2 - Correct recommended level based on peer review summary statement. If no detail was provided for audit in future years summary statement description, unspecified is indicated.

Column 3 - NSABP's final budget request based on NCI funding availability in competing years (CA12027-21 and CA37377-07) or Type 5 commitment level shown on award notice.

Column 4 - NCI's awarded amount based on funding plan level for each year and programmatic review of request.

ATTACHMENT 2

COMPARISON OF AUDIT TRAVEL FUNDS AWARDED TO EXPENDED

PROJECT/YEAR	NCI AWARDED TRAVEL	NSABP EXPENDED TRAVEL	DIFFERENCE
CA12027-21 FY92 (2/1/92 - 1/31/93)	$ 29,389	$21,579.61	$ 7,809.39
CA12027-22 FY93 (2/1/93 - 1/31/94)	26,713	10,035.22	16,677.78
CA12027-23 FY93 (2/1/94 - 4/30/94)	86,851	3,683.44	83,167.56
CA37377-09 FY93 (6/1/93 - 4/30/94)	83,393	64,555.28	18,837.72
TOTAL TRAVEL	$226,346	$99,853.55	$126,492.45

Mr. DINGELL. Now, then there is the next question of did the trials grow too fast? I don't believe that NCI was ever told that NSABP officials were concerned about the rate of recruitment and worried about the effect that this would have on the quality of the work being done; is that correct?

Mr. BRODER. Well, it is very difficult for me to understand that the trials were going too fast. There was a grant put in. The grant was put in by the NSABP to perform a trial.

Presumably, the grantee knows what the grantee is asking in the trial, and that is a point that is a little difficult for me to follow. The trial was to do a major prevention study, and it had expectations and growth.

With the Chair's indulgence, I cannot resist getting back to the budget issue. I apologize. I need to define one point.

At the type two or recompetition phase of a grant, an applicant will come in with a request. I am giving you numbers that are approximate, but they are in the rough ball park. For example, one of NSABP's grants in the prior year, or the last year in the previous cycle might have been $4.5 million, approximately. As they came in for the renewal or recompetition, they may request from us $9 million, or a 100 percent increase. The peer reviewers may cut that to $8.1 million, and since we do not have infinite growth potential we may end up finally giving the NSABP on that grant $6.5 million. Now, $6.5 million is a substantial level of growth compared to $4.5 million, but it is certainly a cut compared to $9 million.

Mr. DINGELL. It is about a 50 percent increase.

Mr. BRODER. Right. So it depends on how you want to look at it.

The final programming of resources within the total award in all of these matters is in the hands of the grantee. The final decision is made when we receive a final NSABP budget request. That is what the grantee is telling us they need, and that was the point you were raising earlier. That is what the grantee is telling us, that they want to do—that is their best determination—and we negotiate. We would always give more flexibility if the grantee asked, and sometimes there is money left over for procedural reasons at the end of a year and they would be most welcome to make a rebudgeting request.

In addition, you should be aware that at the front end of the original request it is not uncommon for the auditing function to be unspecified, and the specification of the amount actually doesn't come in until the final budget negotiations. So I am sorry to have taken your time with the arcana of NIH grants management, but I certainly do not accept the principle that we at NCI inappropriately cut a deserving audit function. I think there was certainly less money to go across the board for all of the research effort, but the exact proportionality that one chooses to commit for budgeting for auditing is in the hands of the grantee. And, finally, as I say, many of the issues that we encountered don't have anything to do with resources.

Mr. DINGELL. Now, there the two other things that we have heard in the questions of the matter before us. One is the request of need for some kind of better management, for example, a director type position that could handle management administration.

Did the people at NSABP ever indicate that they would need some kind of assistance of this sort to handle the trials because they lack the capability to administer the project properly?

Mr. BRODER. No. And Dr. Fisher is a great man and has made great contributions. Anyone who knows NSABP will know that Dr. Fisher is the person who runs NSABP.

Mr. DINGELL. I got sort of the opinion that sometimes maybe it was somebody else running it; I was not altogether clear who was running it at this point.

Mr. BRODER. That is the basis of my statement.

Mr. DINGELL. Now, you heard Dr. Detre earlier this morning about the culture deference given the senior scientists. I think that deference is required, but I am curious, is the deference going beyond their ability to address the problems that they confront in terms of actually administrating a project of this kind?

Mr. BRODER. I think you are raising an excellent point. Inherent in your question is, are the attributes that require creative scientific thinking the very same attributes that are necessary for an executive of clinical trials administration? I think that is a valid point and we are certainly considering it.

I think we may need to look at and pay more attention to the difference between the scientific and creative process, the genius which Dr. Fisher has, and he is a genius, in the development of certain aspects of the scientific outline of a study compared to how one executes that study and how one then pays attention to the incredibly important details that are necessary to make the thing work. And I think that we will certainly look at that issue.

Human nature is difficult to change, and of course if you are in charge of a study, sometimes you want to be in charge of everything, and that is one of the issues we will have to grapple with. But we are certainly looking into whether we should be more effective at circumscribing activities, so that an administrator or administratively oriented person may run the audits and possibly be in charge of certain issues related to quality assurance, and that need not be the same person that develops new scientific ideas, and often wouldn't be. There is no harm or shame in saying that. There is specialization in all fields.

Mr. DINGELL. Thank you, Doctor. Now, Doctor, the last time you were here we discussed the four endometrial cancer deaths in recent treatment trials. I note that there has now been a fifth that has been brought to the attention of NCI through notification. Can you tell us briefly about this particular death and the circumstances that attend it?

Mr. BRODER. We were made aware of an additional death, I believe that came to our attention in May of this year, that apparently had occurred in December of 1993. I would be happy to provide the details for you for the record. I don't know the specifics of how the case was diagnosed.

Mr. DINGELL. Well, it appears that the NSABP learned of it in April, as a matter of fact April 8 of 1994, and they informed the NCI of it the first week in June. Is that right?

Mr. BRODER. I thought it was May, but it—I have staff here who could answer that question.

Mr. DINGELL. You would know better than I would.

Mr. BRODER. I apologize. It was June 3rd. You are quite correct. June 3rd.

Mr. DINGELL. Doctor, it is always a privilege to have you here before the committee. I want to express my thanks to you, my commendations of the fine job you are doing.

I would like to have a few concluding remarks. First to you, Dr. Broder, congratulations, and both for your testimony and for your leadership in this area. We think that it is important that you continue to do so, because it is not the business of this committee to try and be the policeman of science; we want the scientists to do that themselves rather than us.

To Doctors O'Connor, Herberman, and Detre, I want to commend you for your testimony today, gentlemen. I know it was not an easy day for you, and it is not the practice of this committee to make our days easy for our witnesses. But your testimony indicates that you have a solid understanding of the portions that contribute to the misfortunes in the NSABP matter, as well as remedial actions that need to be taken to make this institution a responsible, productive enterprise once again, and I commend you for that.

We will observe the continued developments in this matter, in particular the implementations of the promised reforms with great interest, and we express to you our good wishes that you be successful in that, because it is important.

You come from a great institution, one of which you are justifiably proud, and I know you want to make it better, and it is the good wishes of this committee that you shall be successful in making it better.

We hope that this whole matter will now be brought to a happy conclusion, because we know the importance of the work that is being done here, and to the surprise of some in the scientific community, this committee, this subcommittee, and this particular chairman have spent a great deal of time and effort and money to see to it that NIH is a success, it is adequately funded, that you scientists and educators and research specialists of different kinds are successful in your understanding because they are very important to us and to the country.

So we express our thanks to all who assisted us today. We commend our witnesses; we give them our good wishes for continued success, and we call the committee to an adjournment.

[Whereupon, at 4:03 p.m., the hearing was adjourned.]

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